Modulating the Immune Response to Fight Prostate Cancer – How to Maximize a Minimal Outcome

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Rationale for Vaccines in Prostate Cancer

1. Well-characterized glycoprotein and carbohydrate antigens: PSA, PSMA, PSCA, ACP, Globo H, GM2, Lewis^{y}, MUC-1,2, Tn, TF

2. Multiple ways of breaking immunologic tolerance :
   [viral vectors – fowlpox, VEE, adeno +/- prime boost]

3. Modulation of immune response via cytokines (GM-CSF) and immunomodulatory molecules (CD40, CTLA-4)

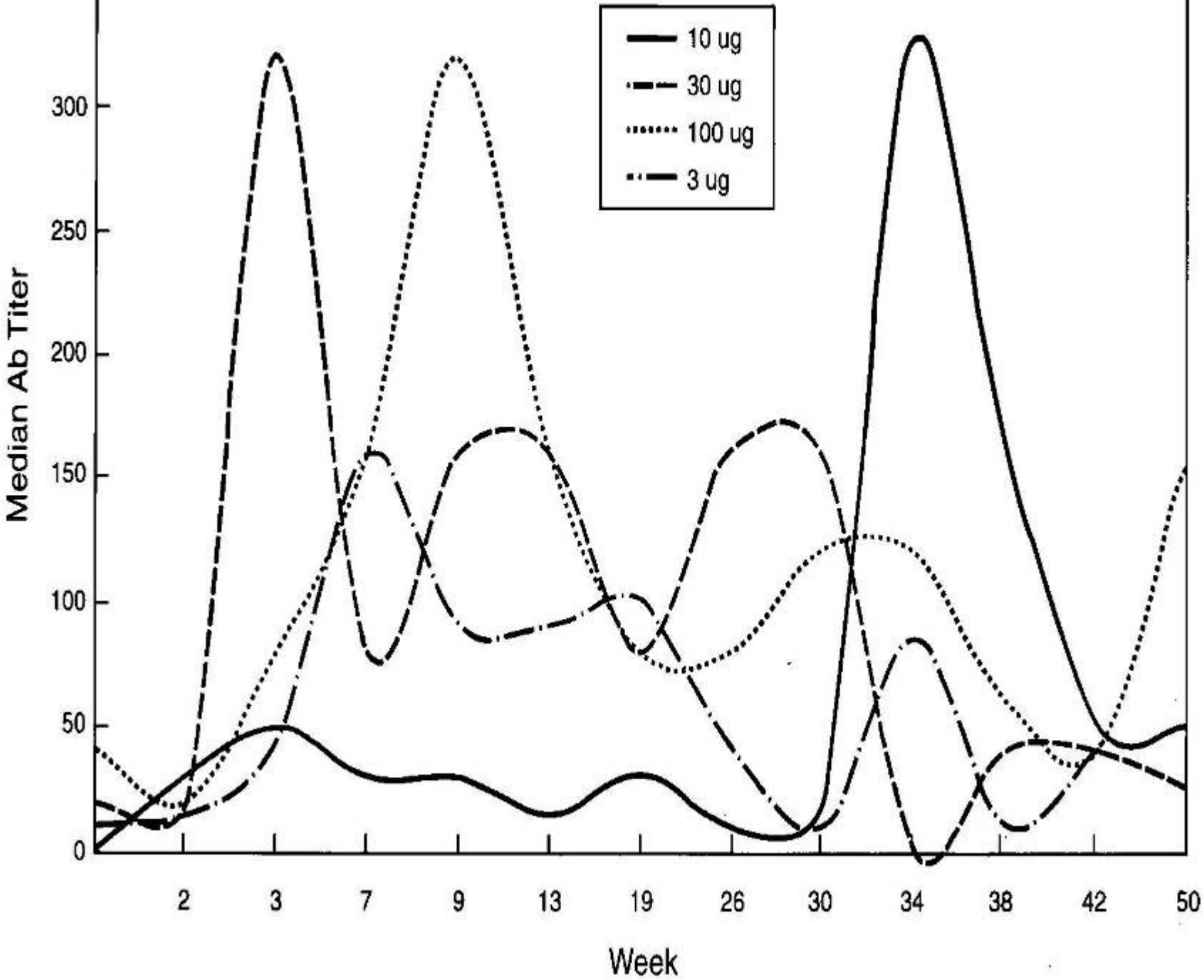
4. Minimal toxicity [skin]

5. Can be used in a minimal disease state prior to development of metastatic disease.

6. Biomarker available to study disease progression.

What have we learned from prostate cancer vaccine trials?

1) Chemical mimes of known cell surface molecules were immunogenic
2) Role of carriers and adjuvants to enhance immunogenicity; change in conformation can affect immunogenicity
3) ↑ doses of vaccine did not correlate with augmentation of immunogenicity, ie, lower doses appear to be more immunogenic
4) Specific Abs were induced but ***no*** way to potentiate T cell responses
5) Immunologic responses - not immediate ; no role for boosters unless they were given frequently.
6) Δs in pre- vs posttreatment PSA slopes - no major impact on pts with high risk disease destined to progress within two years.


10 ug
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Median Ab Titer
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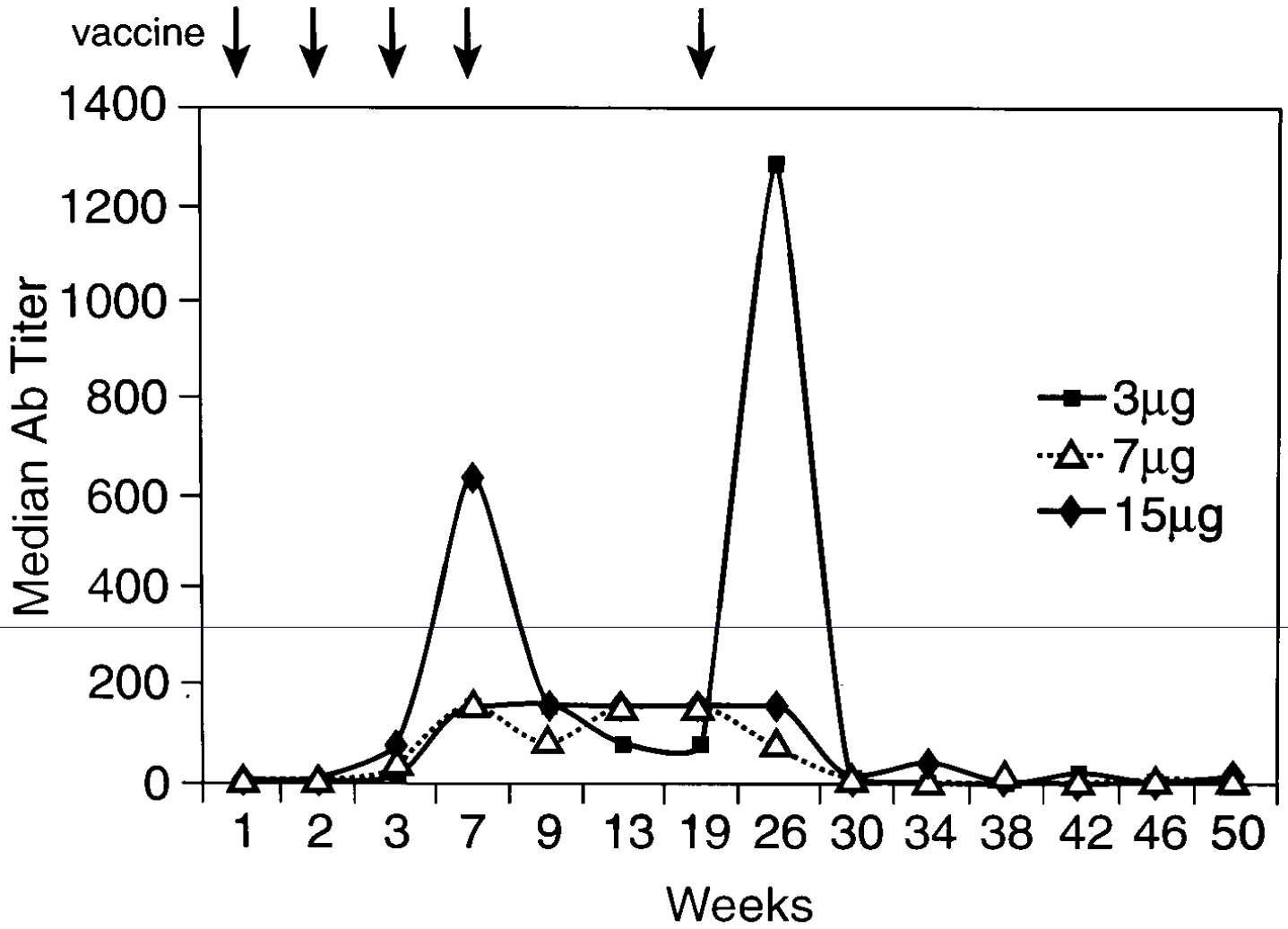
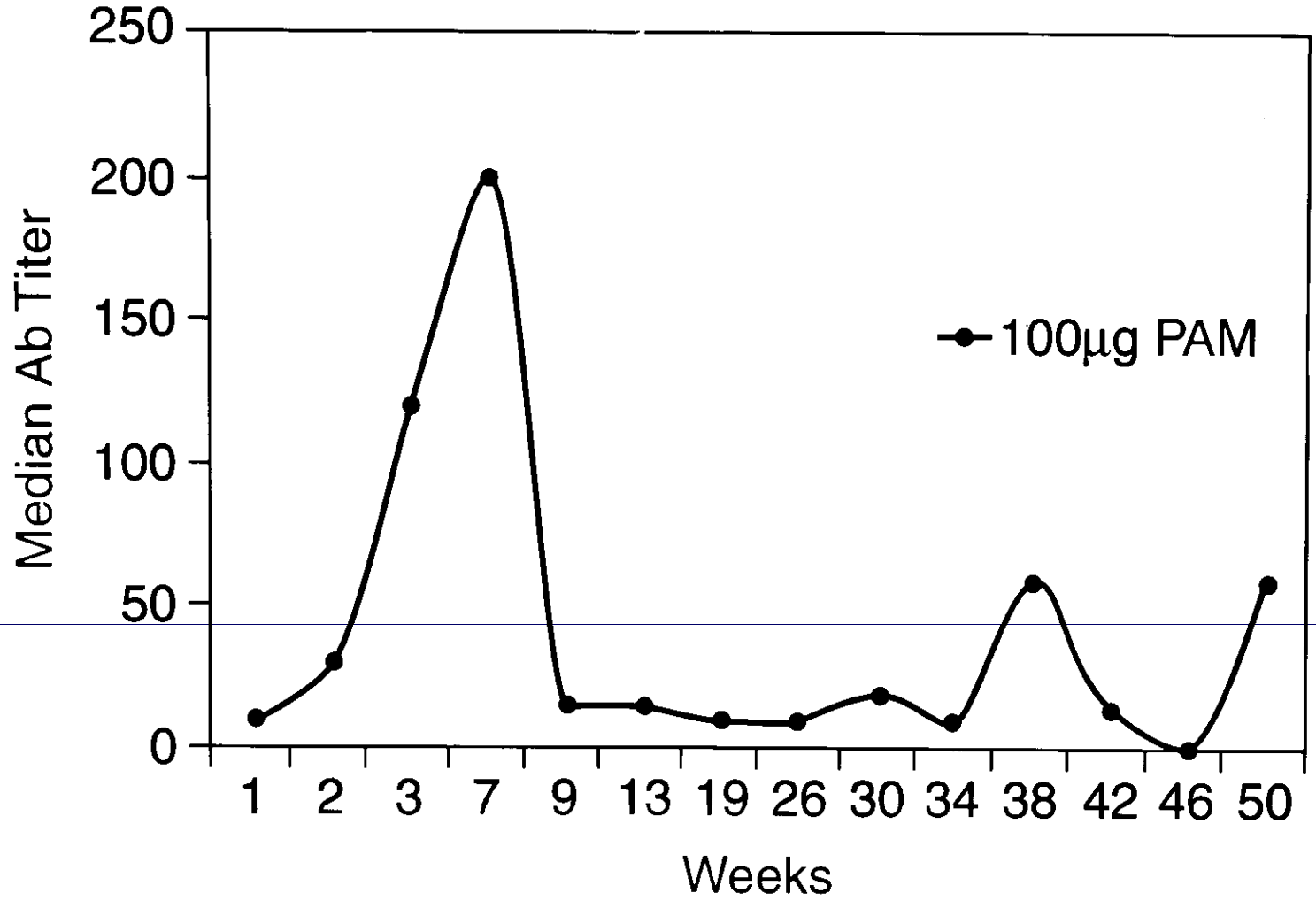
Week

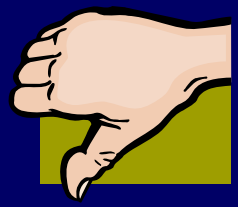
Median IgM Antibody Titers: Tn(c)-KLH-QS21 Vaccine



Median IgM Antibody Titers: Tn(c)-PAM-QS21 Vaccine



Do we need to change our current paradigms in designing immune-based clinical trials?



Sufficient data now exist that we can generate humoral/cellular responses; our immune read-outs correlate clinically

Despite immune “responses”, the target is ***not*** really “hit” and we are not getting a direct correlation between development of humoral/cellular immunity and clinical benefit

Why have we not succeeded, if …?

1) Evidence of immunogenicity is confirmed, i.e., induction of specific effector populations, Treg, DC
2) Can modulate immune system with cytokines or checkpoint inhibitors
3) Vaccine is safe
4) Impact in PSA doubling time or slope
5) May result in stable “disease”
6) But, clinical benefit uncertain

The Issues…

- Defining the immunologic target and establishing the most appropriate screening assays that will allow a “go/no go” approach for a vaccine trial which demonstrates that the target has been recognized.

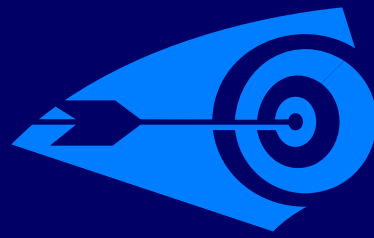
- Concerns that bystander effects may prevail such that a clinical response is obtained in the absence of a documented immunologic response

- How do we address the differences than an *in vitro* immune responses (Ab, T cells), may not correlate with a true antitumor response?

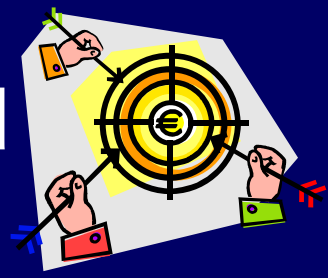
- How do we establish relevance of immune responses with clinical outcome? Are the current “standards” below the limits of detectability of the assays and should the actual tumor be further examined for true immunologic response?

Results of Clinical Trial Endpoints

- Tumor responds - target is hit

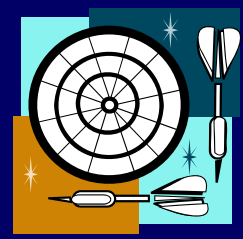


- Tumor responds - target is missed



- Tumor ≠ respond - target is hit

- Tumor ≠ respond - target is missed

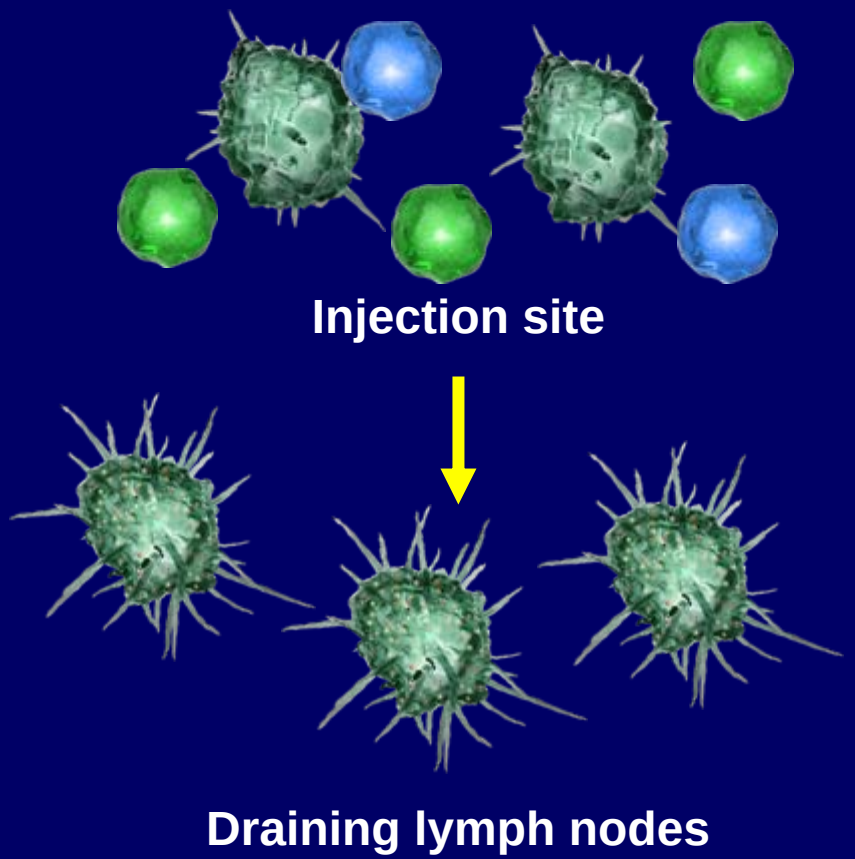


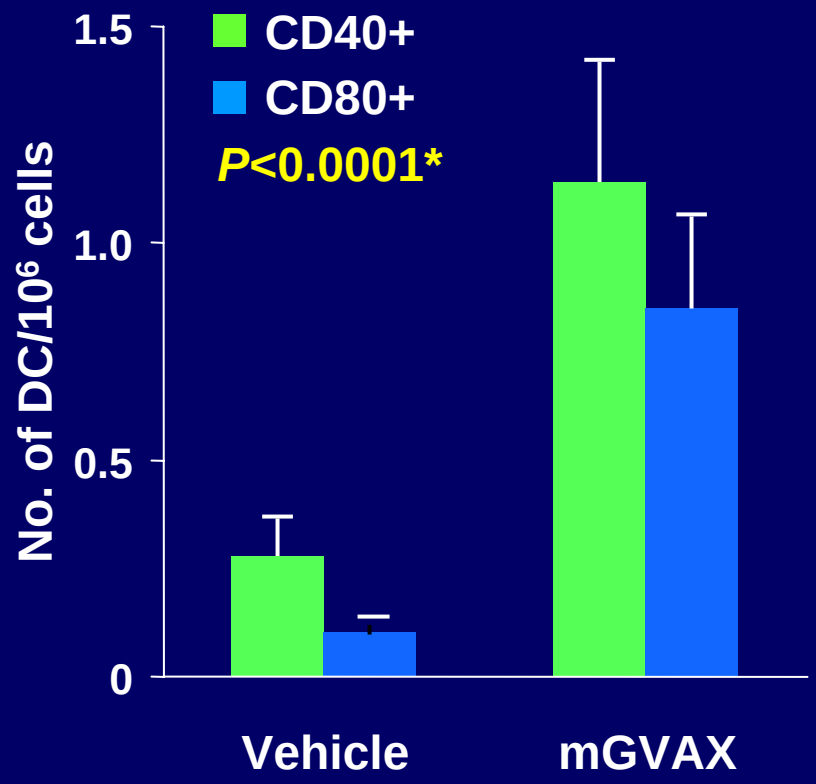
All say something about the biology of the tumor and how the therapy should be directed

APPROACHES FOR INDUCTION OF IMMUNITY

Techniques	Immunologic Response
Insertion of cytokine genes - ***cytoreductive*** approach	Enhances anti-tumor response by T lymphocytes
Gene modification of adoptively transferred T cells	Maintains effector cells *in vivo,* may used to deliver toxic agents
Use of suicide genes - ***corrective*** approach	Specifically targets tumor cells using antitumor promoters, rapid delivery
Antisense or Ribozymes	Suppresses or deactivates oncogenes
Genetic alteration of stem cells agents;	May ☑ heme toxicity from chemo may ↳ T cell progeny

mGVAX Treatment Increases Activated DC in the Draining Lymph Nodes in Preclinical Models

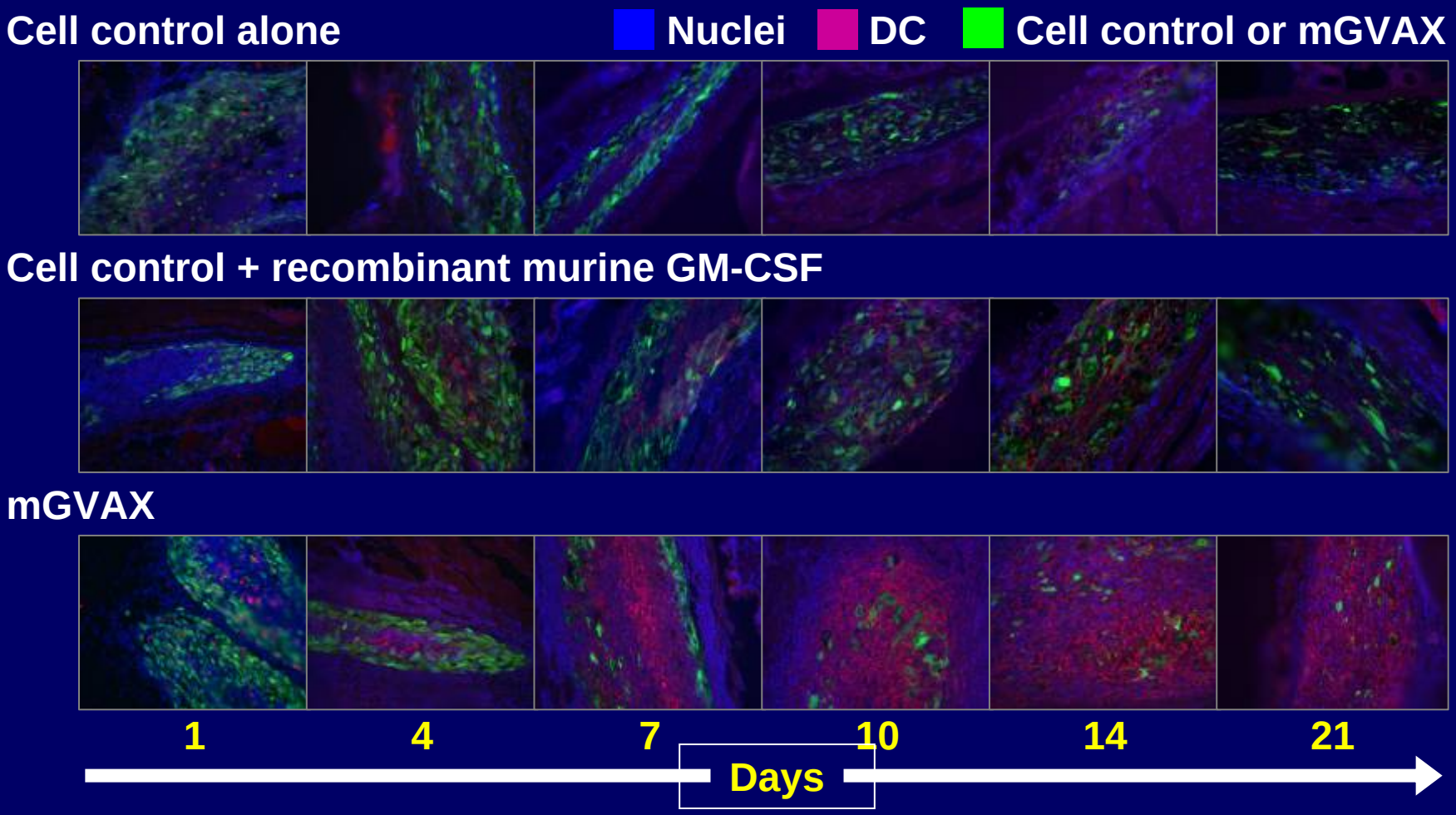




*P<0.0001 for vehicle vs mGVAX for CD40+ DC and for CD80+ DC.

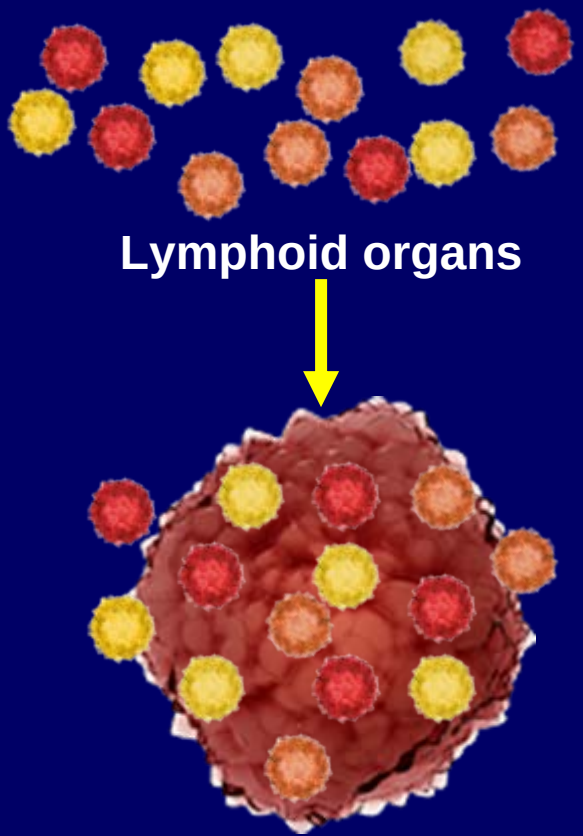
Data on file, Cell Genesys, Inc.

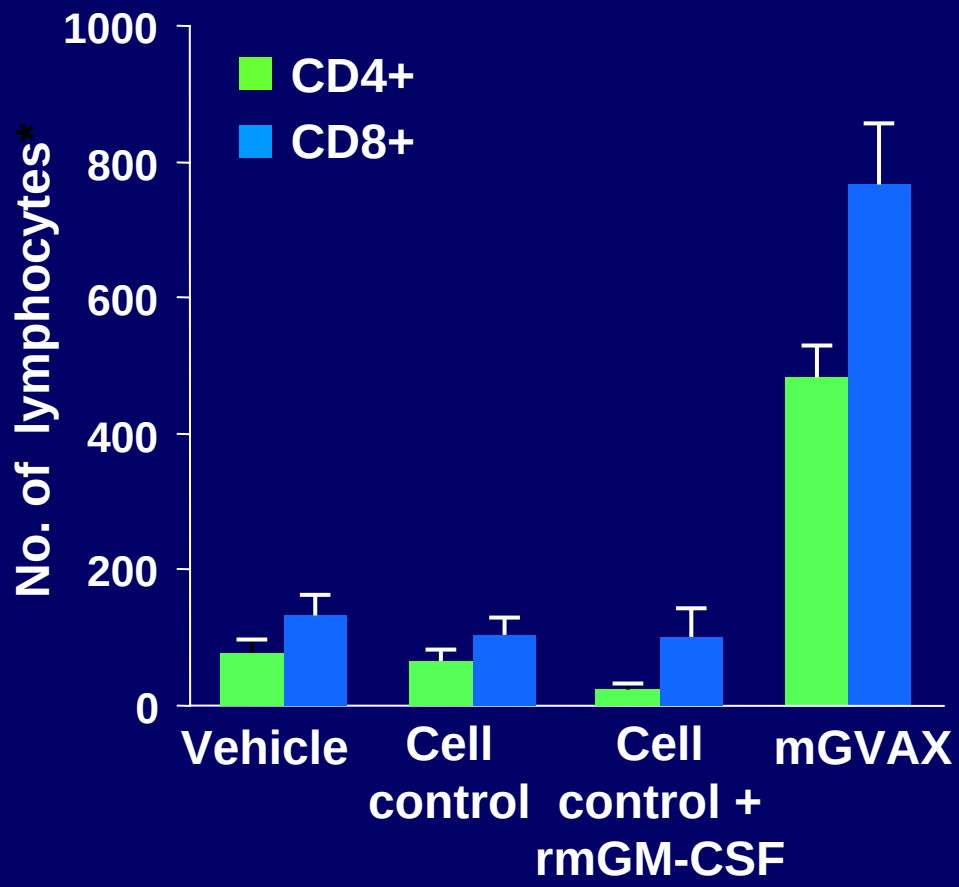
mGVAX Treatment Leads to Durable DC Infiltration at the Injection Site in Preclinical Models



Data on file, Cell Genesys, Inc.

mGVAX Treatment Increases Activated Tumor-Infiltrating Lymphocytes in Preclinical Models

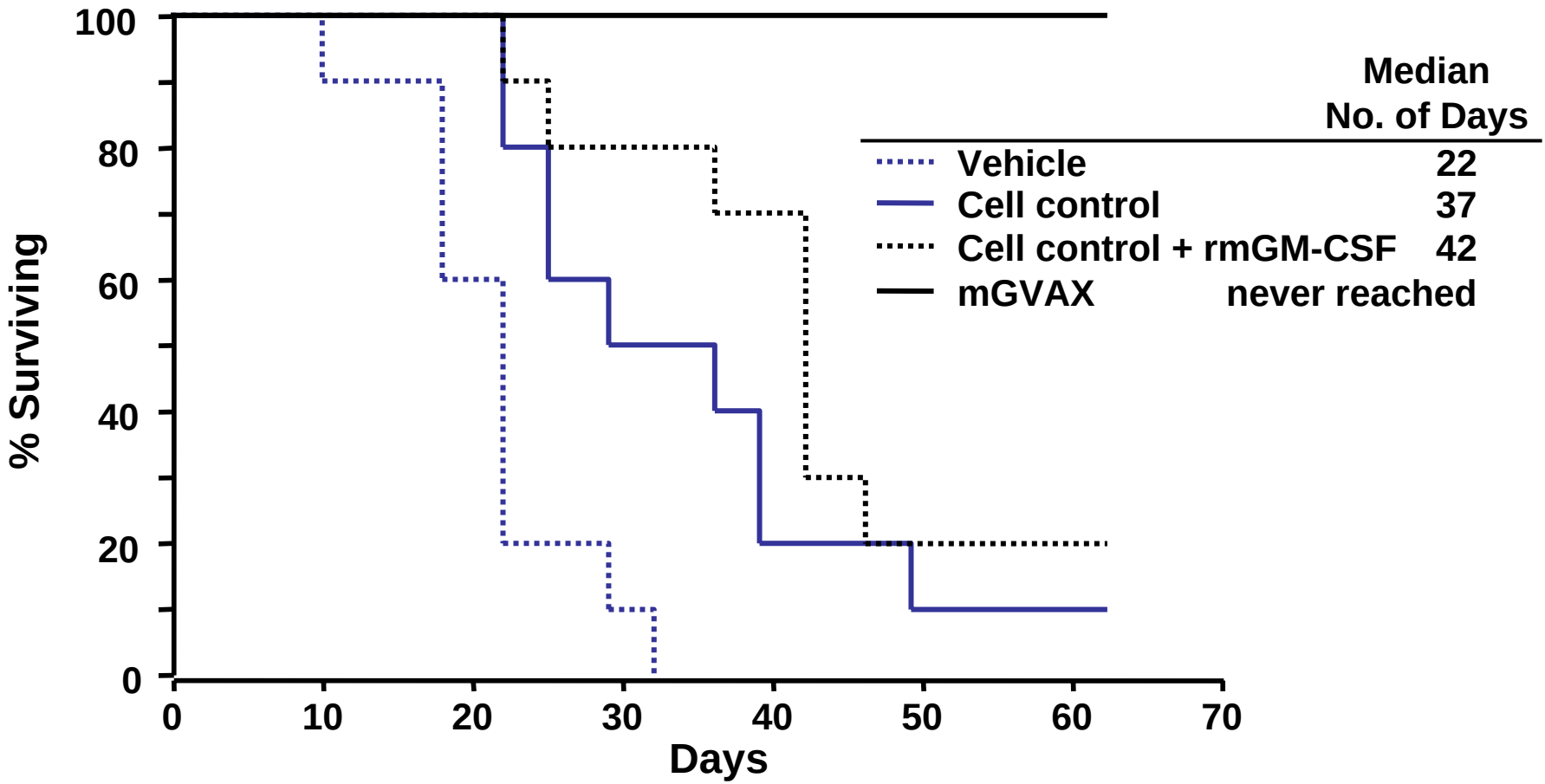




*No. of activated CD4+ or CD8+ cells per 10^6 tumor cells 24 days after administration of mGVAX.

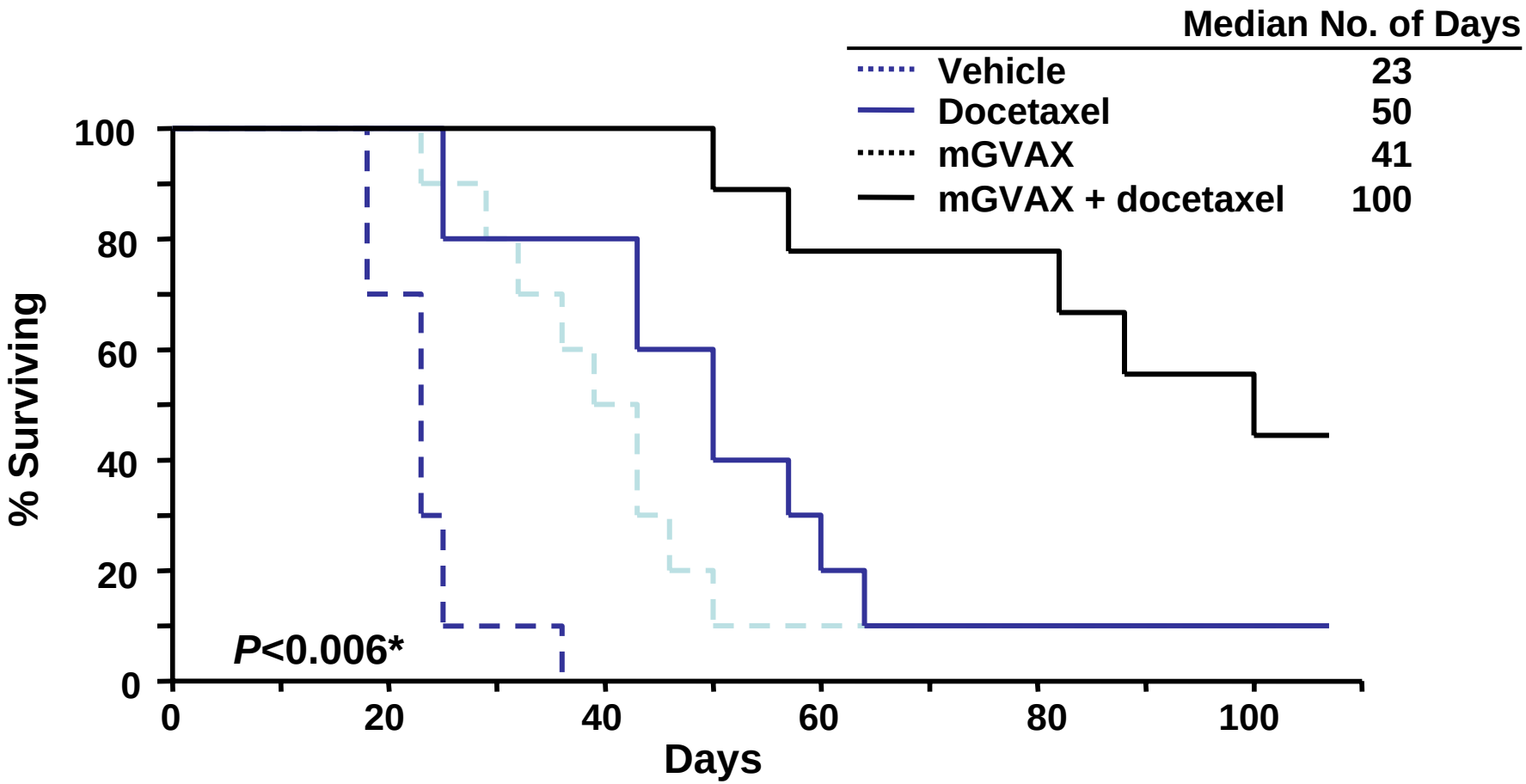
Data on file, Cell Genesys, Inc.

mGVAX Improves Survival in Preclinical Prevention Models



Data on file, Cell Genesys, Inc.

Addition of Docetaxel to mGVAX Improves Survival in Preclinical Treatment Models

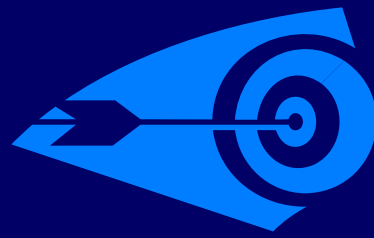


*P value for mGVAX + docetaxel vs all other treatment groups.

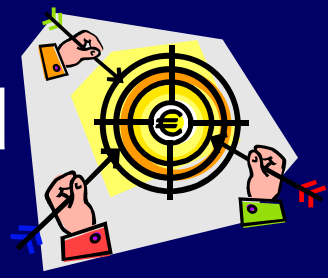
Prell et al. *Cancer Immunol Immunother*. 2006. Epub ahead of print.

Results of Clinical Trial Endpoints

- Tumor responds - target is hit



- Tumor responds - target is missed



- Tumor ≠ respond - target is hit

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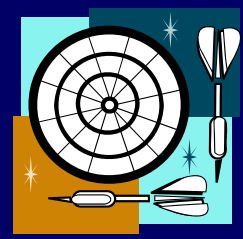


All say something about the biology of the tumor and how the therapy should be directed

Problems…

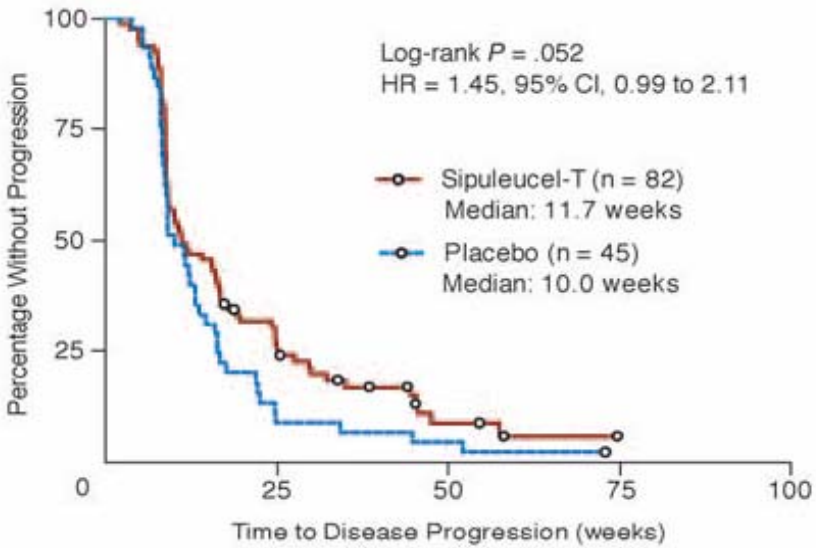
"*I don't want to hear about the problems, only the solutions!*"

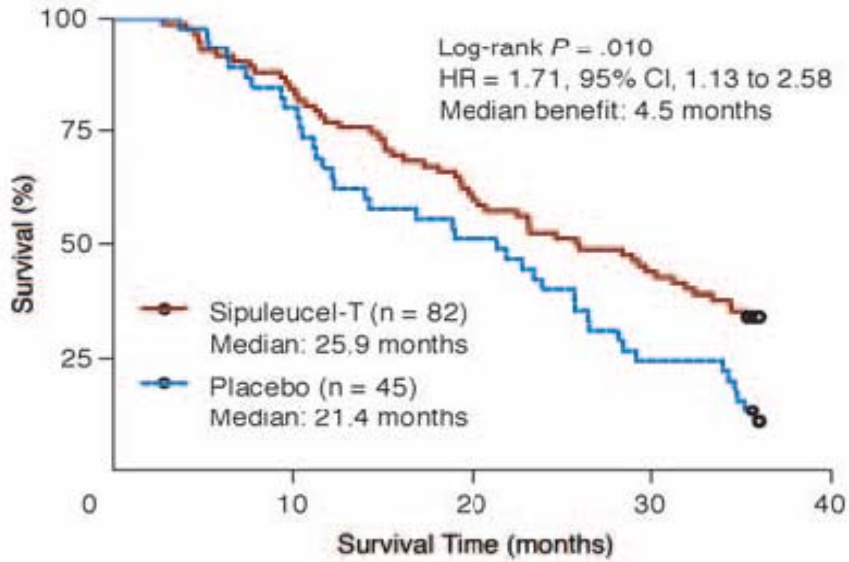
- How to ensure target is hit
- Are we targeting one antigen but impacting on another
- How to reconcile differences in clinical vs immunologic response
- Standardization and harmonization of immune assays ["immune monitoring"]
- Establishing endpoints which FDA will accept

- Assays currently available:
-
- Human:
- - Peptide ELISPOT (IFN-g 9-mer, HLA-A.2)
- - IL-5 ELISPOT
- - Tumor Cell ELISPOT
- - Granzyme B ELISPOT
- - Cytokine Induction
- - Proliferation
- - 51Cr release cytotoxicity
- - Cytotoxic T-lymphocyte induction
- - Whole Protein ELISPOT
- - DC generation
- (IFN-g and IL-5 with or without DC)
- Currently working on optimizing human perforin and B cell ELISPOT a assays
-
- Murine:
- - IFN-g ELISPOT
- - IL-2 ELISPOT
- - IL-5 ELISPOT
- - GM-CSF ELISPOT
- - MCP-1 ELISPOT
- - Granzyme B ELISPOT
- - Cytotoxic T-lymphocyte induction
- - Flow cytometric-based cytotoxicity
- Currently working on optimizing a murine IL-17 ELISPOT assay
-
- Non-human primate:
- IFN-g ELISPOT
- Note: ELISPOT assays can be performed on PBMC, purified CD4+ or CD8+ T cells, in vitro stimulated CTL, or NK cells.

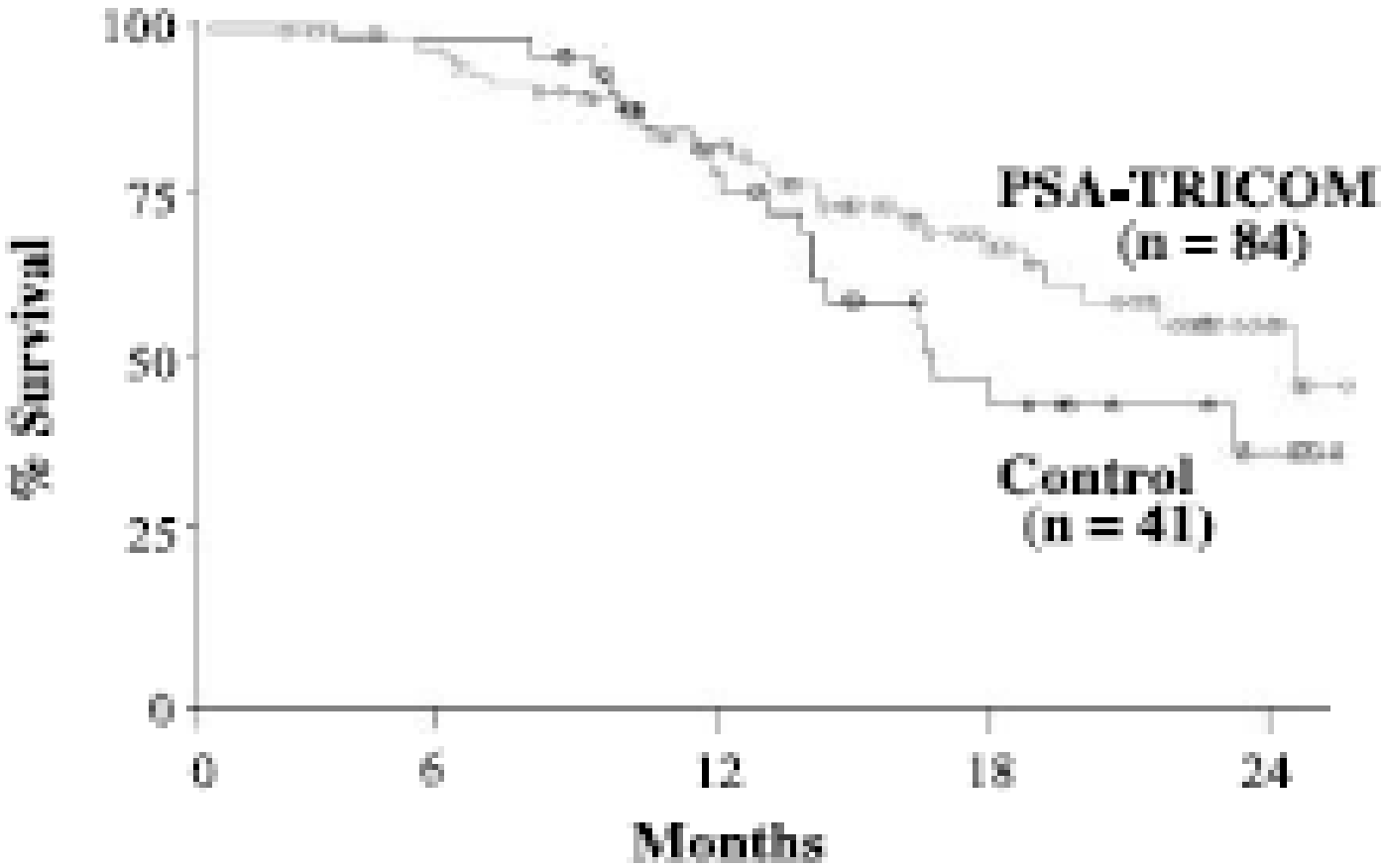
“treat” or “not treat” by example

- Provenge™
- G-VAX™
- Tri-Com
- Onyvax-P
- Polyvalent glycoprotein/carbohydrate
- Xenogeneic DNA





Small, et al, JCO, 2006



Median Overall Survival:

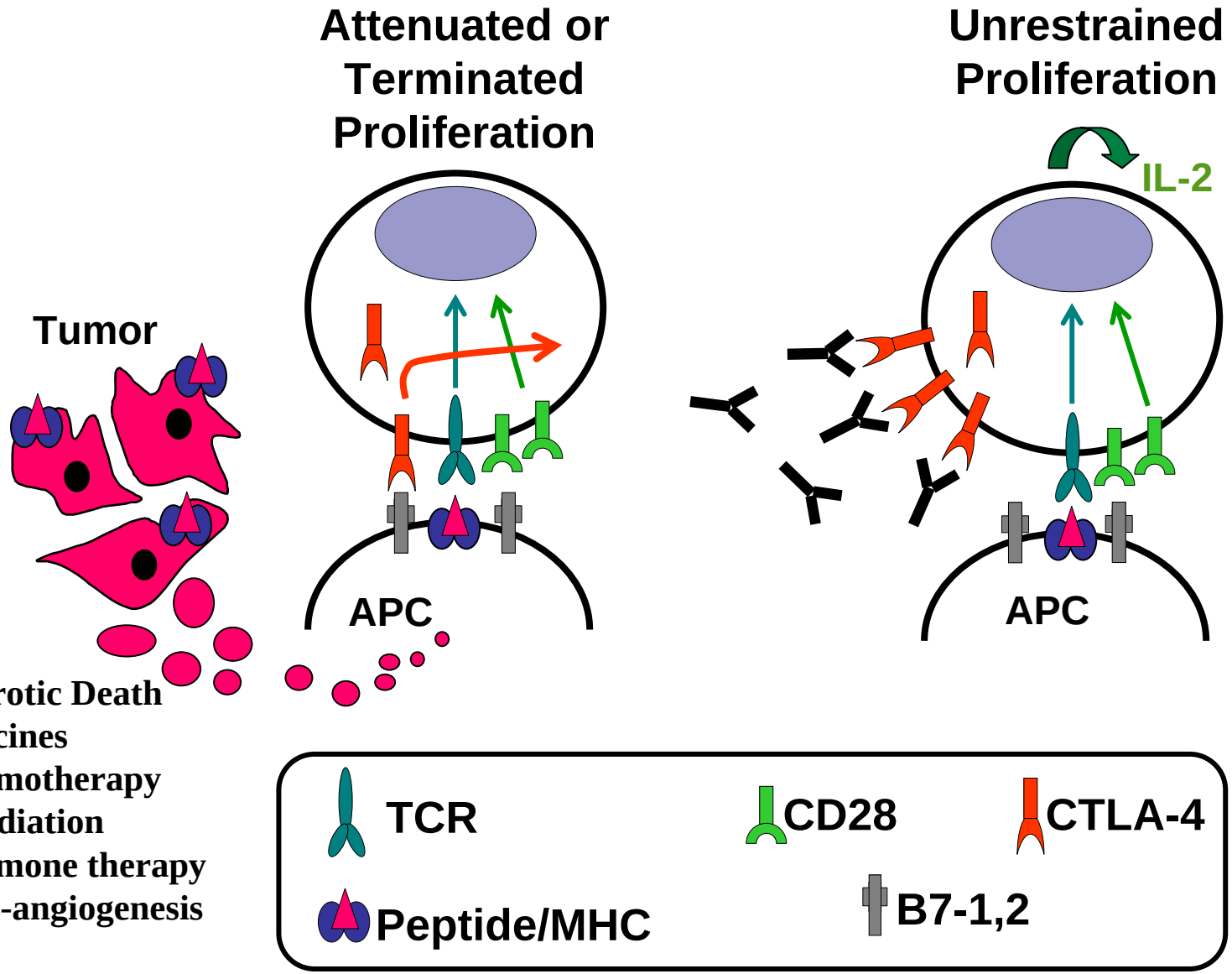
Control vector	16.3 months
PSA-TRICOM	24.4 months

Kantoff, Proc Amer Soc Clin Onc, 2006

How can we maximize an otherwise weak or poorly measurable immune response?

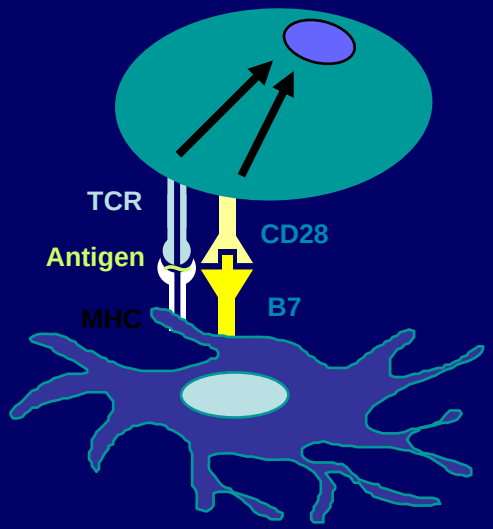
- Cytokines
- Release of check-point inhibitors
- Inhibitors of immunologic “brakes” within the system or “give it the gas” types of strategies,
- Consider pretreatment immunosuppressives, ie cyclophosphamide

CTLA-4 Blockade
Enhances Tumor-Specific Immune Responses



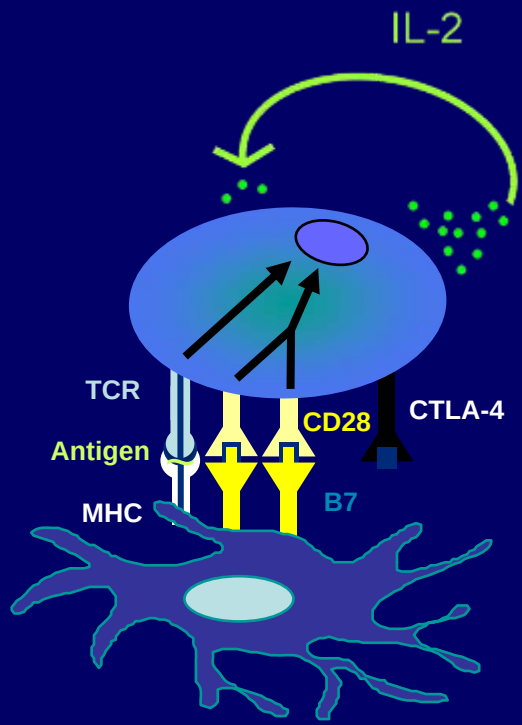
Leach & Allison
Science 1996

Regulation of T cell activation



Antigen-specific T cell Activation

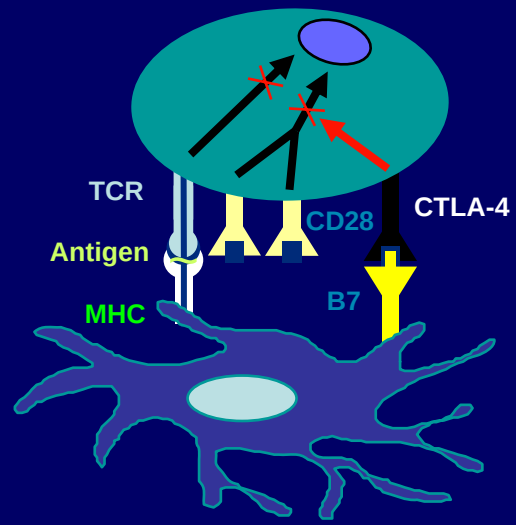
- TCR : Antigen MHC
- CD28 : B7 Co-stimulation



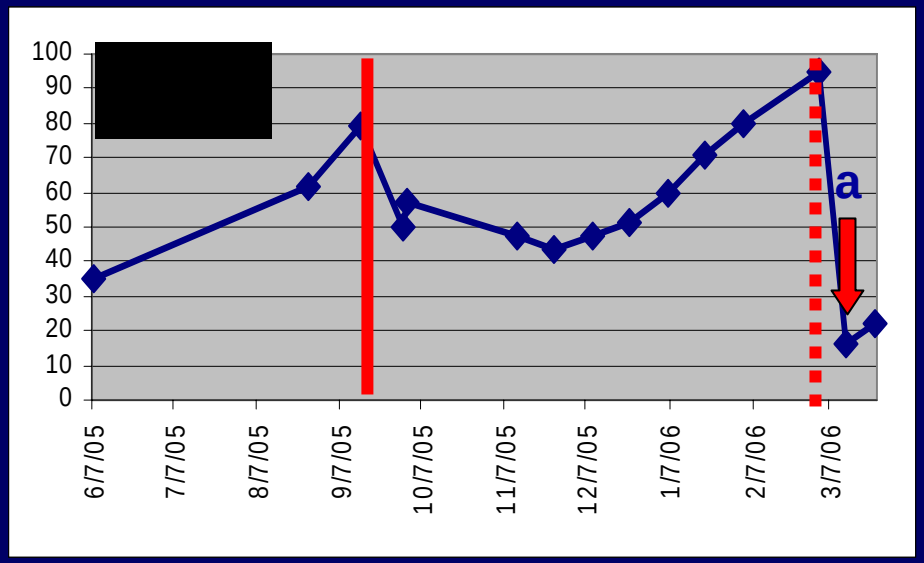
Activated T cell

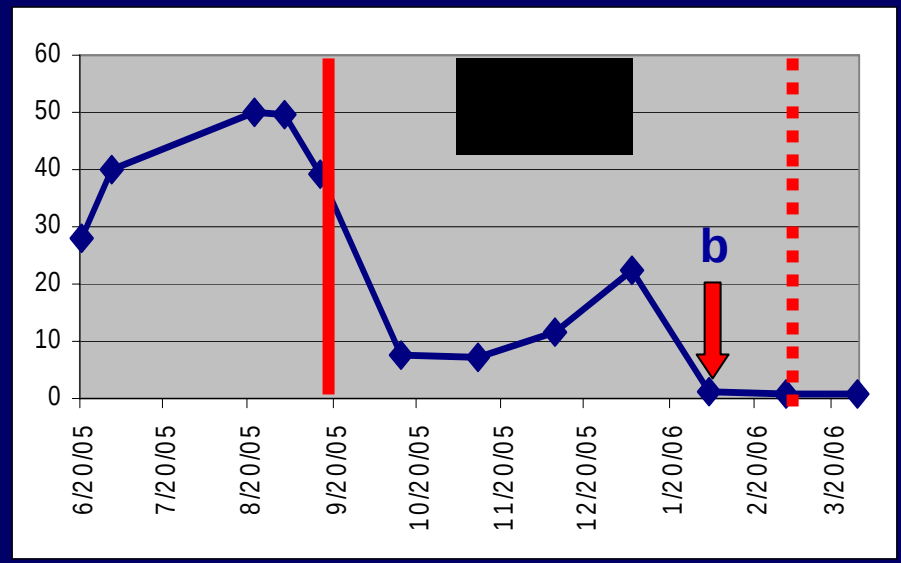
- IL-2 secretion
- Proliferation
- Effector function
- Induction of CTLA-4

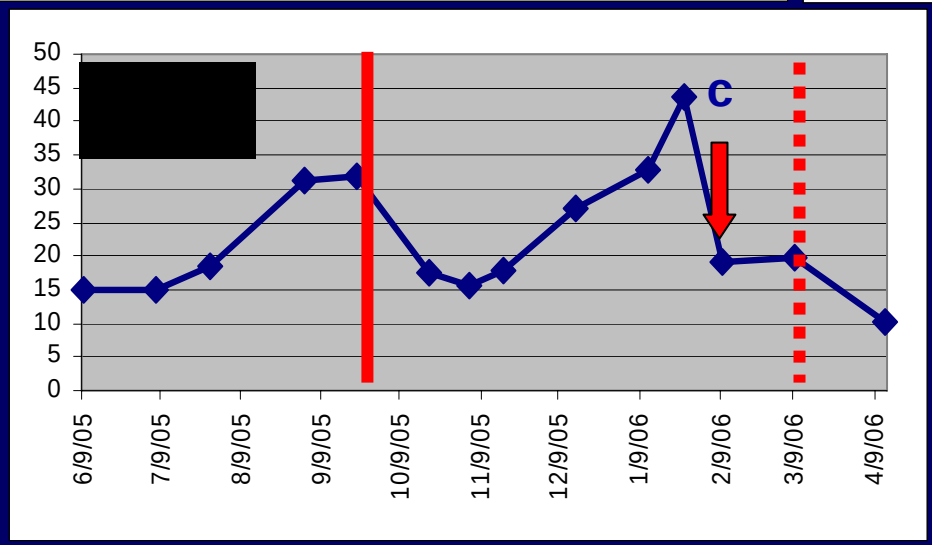
- **CTLA-4 : B7 suppression**
- **Termination of response**



PSA curves – Dose Level 3 (3 mg/kg)







a : 13Mar06: SAE -Hypophysitis (7 mo)

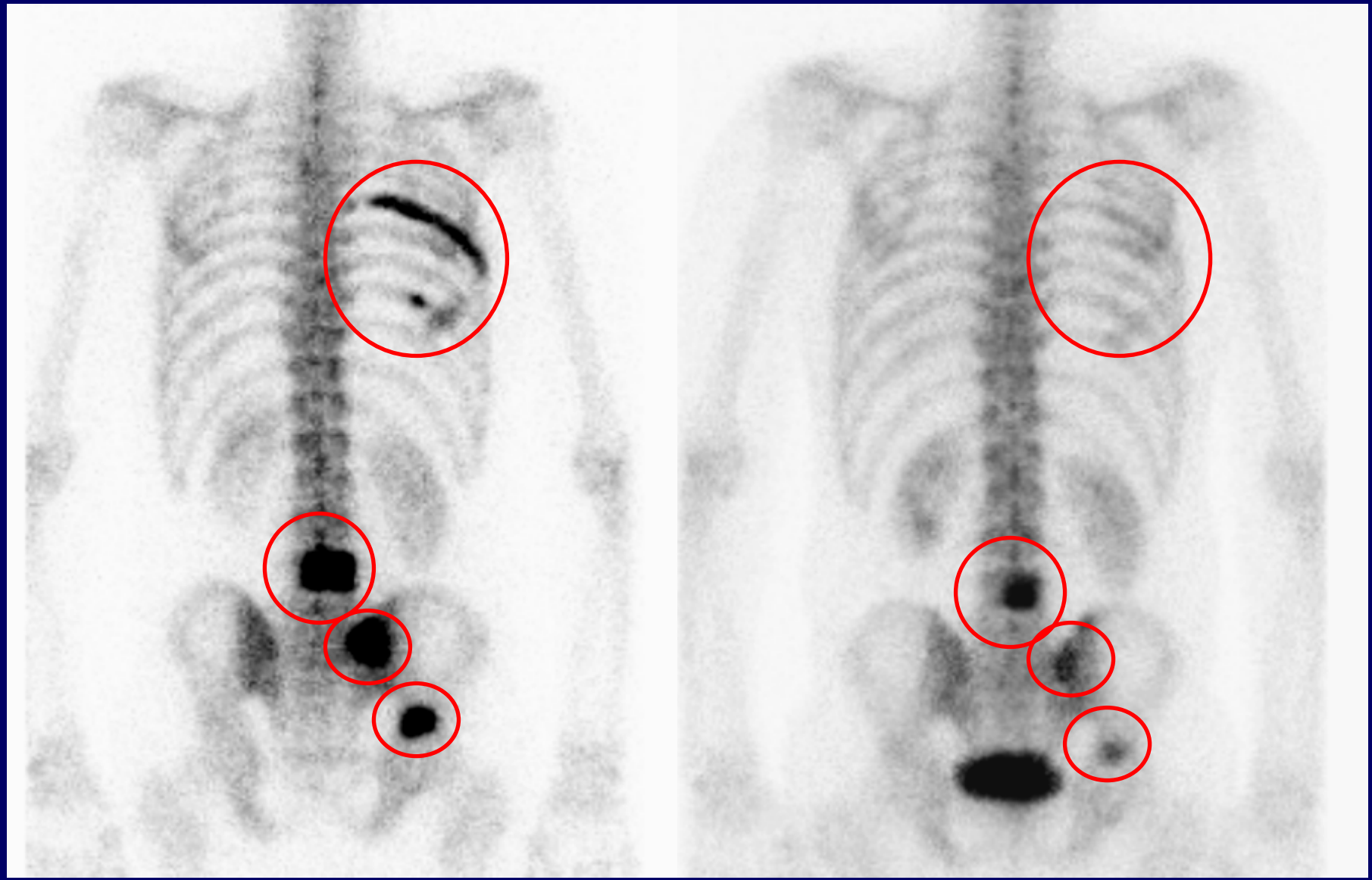
b: 03Feb06: Hypophysitis (5 mo)

c: 09Feb06: SAE – Hypophysitis (5 mo)

Gerritsen, ASCO 2006

Patient 8

Bone Scan Improvement in Patient 8 (3 mg/kg)



15Sept05

Gerritsen ASCO2006

29Mar06

Changing Paradigms

- Adoptive immunotherapy +/- cytokines

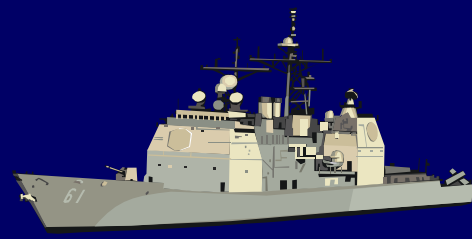
- Single agent vaccines:

- enough or just sufficient?

- Combinatorial approaches:

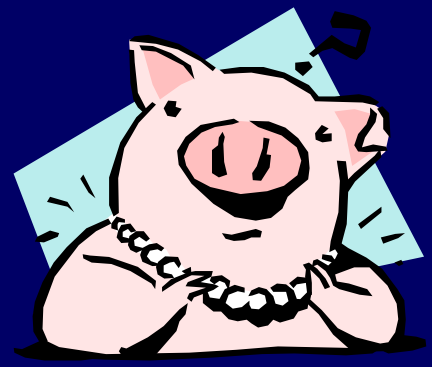
- Irradiated tumor cells [antigen integrity]
  +/- cytokine(s)/immunomodulatory molecules [B7.1]
- Synthetic proteins/peptide/DNA +/- adjuvants
- Checkpoint inhibitors +/- vaccines
- Prime boost
- Vaccine + chemotx

Are we missing the boat?



- Timing off?
- Subclinical/immunologic response [not detected by current assays]
- Role of boosters
- Target antigens
- Unacceptable trial designs
- “Right” or “Wrong” disease state

The Prostate Immunotherapy Group (PIGs)



Spokesperson: Susan Slovin, MD, PhD

Genitourinary Oncology Service

Sidney Kimmel Center for Prostate and Urologic Cancers

Memorial Sloan-Kettering Cancer Center

New York, NY

What is the “PIGs”?

- A consortium of academia, industry and participating governmental agencies (NCI, DOD, FDA) whose tasks encompass:

  1) Developing scientifically meaningful immunologic endpoints for vaccine/immunotherapy trials which can be broadly applied in a standard manner for all immune based trials;

  2) Establishing a standardized panel of immunologic assays and metrics, through collaboration, for immune monitoring which can be used to assess treatment response;

  3) To foster the development and facilitate the activation of immunotherapy trials through the DOD prostate cancer consortium which will impact on prostate cancer patient care and ensure a mechanistic understanding of patient benefit;

  4) Establish standardized recommendations for publication which reflect the necessary correlative studies that can be used in immunotherapy clinical trials.

Meeting: **Inaugural Meeting of the Prostate Immunotherapy Group (PIGs)**

Site: **Chicago Hilton Hotel, Chicago, IL**

Date: **May 31, 2007**

Sponsor: **Prostate Cancer Foundation (PCF)**

Attendees: James Allison, PhD (MSKCC), Douglas McNeel, MD, PhD (U. Wisconsin), Philip Arlen, MD, PhD (NCI), James Gulley, MD, PhD (NCI), Charles Drake, MD, PhD (Johns Hopkins), Eric Small, MD (UCSF), Larry Fong, MD, PhD (teleconferenced, UCSF), Chung Lee, PhD (Northwestern Medical Center), Sylvia Janetzki, MD (Zellnet, Inc; Chair, Assay Working Group, CVC), Pam Sharma, MD, PhD (MD Anderson), Neil Bander, MD (Weill Medical College, Cornell University, New York Presbyterian-Hospital), Howard Soule, PhD (PCF), Jonathan Simons, MD (PCF), Susan Slovin, MD, PhD (MSKCC)

Conclusions

- Greater awareness of need to standardize immune monitoring – e.g., seromics?
- Improving trial design to address both clinical and research questions
- Standardization of trial endpoints by nature of the therapy
- Combinatorial strategies more appealing but immune assays ***must*** be target-specific

Thank you