# Current Tumor Immunotherapy

Part 1: On the preclinical and clinical efficacy of the "current cancer vaccines."

Part 2: The critical role of cancer vaccines in new integrative approaches.

# The State of the Art:
# Tumor Immunotherapy

It is possible to cause tumor regression using purely immunological manipulations. There is now are now at least three examples where immunotherapy has shown efficacy using standard oncologic criteria:

1. Recombinant Interleukin-2 (IL-2).

2. Anti-CTLA-4 monoclonal antibody.

3. Adoptive Cell Transfer (ACT) of anti-tumor T cells given in combination with IL-2.

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PERSPECTIVE

**10**, 909 - 915 (2004)

# Cancer immunotherapy: moving beyond current vaccines

Steven A Rosenberg, James C Yang & Nicholas P Restifo

**• We summarized our experience designing, building and testing cancer vaccines pre-clinically and in more than 3 dozen clinical trials with 541 vaccine treatments in patients.**

**•We found that the objective response rate was low (2.6%) and comparable to the results obtained by others.**

**• We advocated for the development of new vaccine approaches and reaffirmed our own ongoing commitment to cancer vaccine development.**

To many immunotherapists, cancer vaccines seem like a good idea.

They should work . . .

How do we reconcile differing perceptions regarding the therapeutic effectiveness of cancer vaccines?

But first, let's look at the numbers . . . .

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# Overall objective response rate of 1.9%* in cancer patients receiving recombinant virus or “naked DNA”-based regimens our clinical trials

| Virus | HLA restriction | Total patients | NR | PR | CR |
|---|---|---|---|---|---|
| Fowlpox MART-1 | Any | 12 | 12 | 0 | 0 |
| Fowlpox gp100 | Any | 20 | 20 | 0 | 0 |
| Fowlpox gp100(210M, 288V) | A2 | 15 | 14 | 1 | 0 |
| Fowlpox gp100($ES_{209\ 271}$(210M)) | A2 | 46 | 46 | 0 | 0 |
| Vaccinia MART-1 | Any | 5 | 5 | 0 | 0 |
| Vaccinia gp100 | Any | 16 | 16 | 0 | 0 |
| Adenovirus MART-1 | Any | 17 | 16 | 0 | 1 |
| Adenovirus gp100 | Any | 7 | 7 | 0 | 0 |
| DNA gp100(210M, 288V) | A2 | 22 | 21 | 1 | 0 |
| **Total** | | **160** | **157** | **2** | **1** |

Rosenberg, Yang & Restifo, 10, 909 - 915 (2004)

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# Overall objective response rate of 2.9% in cancer patients receiving peptide vaccines in our clinical trials

| Peptide | HLA restriction | Total patients | NR | PR | CR |
|---|---|---|---|---|---|
| MART-$1_{27\ 35}$ | A2 | 23 | 22 | 1 | 0 |
| MART-$1_{27\ 35}$ + IL-12 | A2 | 12 | 12 | 0 | 0 |
| MART-$1_{26\ 35}$(27L) | A2 | 6 | 6 | 0 | 0 |
| TRP-$2_{180\ 188}$ | A2 | 20 | 19 | 1 | 0 |
| $gp100_{209\ 217}$ | A2 | 9 | 8 | 0 | 1 |
| $gp100_{209\ 217}$(210M) | A2 | 32 | 32 | 0 | 0 |
| $gp100_{209\ 217}$(210M) + IL-12 | A2 | 28 | 28 | 0 | 0 |
| $gp100_{209\ 217}$(210M) + GM-CSF | A2 | 18 | 18 | 0 | 0 |
| $gp100_{280\ 288}$ | A2 | 9 | 9 | 0 | 0 |
| $gp100_{280\ 288}$(2889V) | A2 | 5 | 5 | 0 | 0 |
| $gp100_{154\ 162}$ | A2 | 10 | 0 | 0 | 0 |
| gp100ES:$_{209\ 217}$(210) | A2 | 9 | 9 | 0 | 0 |
| g209-2M + MART-27L | A2 | 23 | 23 | 0 | 0 |
| g209M, g280V, MARTL + t3D | A2 | 16 | 14 | 2 | 0 |
| $gp100_{44\ 59}$ | DR4 | 4 | 4 | 0 | 0 |
| $gp100_{44\ 59}$ + g209M + MART | A2/DR4 | 22 | 21 | 0 | 1 |
| $Tyrosinase_{240\ 251}$ | A1 | 16 | 15 | 1 | 0 |
| $gp1001_{7\ 25}$ | A3 | 12 | 12 | 0 | 0 |
| $Tyrosinase_{206\ 214}$ | A2 | 8 | 8 | 0 | 0 |
| TRP-1 ORF1 9 | A31 | 5 | 5 | 0 | 0 |
| Combination peptides | Non-A2 | 15 | 15 | 0 | 0 |
| MAGE-$12_{170\ 178}$ | Cw7 | 9 | 8 | 1 | 0 |
| NY-ESO-$1_{157\ 165}$(165V) | A2 | 19 | 19 | 0 | 0 |
| NY-ESO-$1_{161\ 180}$ | DP4 | 6 | 5 | 1 | 0 |
| NY-ESO-$1_{161\ 180+157\ 165}$(165V) | A2/DP4 | 11 | 11 | 0 | 0 |
| Her2/$neu_{369\ 378}$ | A2 | 6 | 6 | 0 | 0 |
| $Telomerase_{540\ 548}$ | A2 | 13 | 13 | 0 | 0 |
| Dendritic cells + g209M + MART | A2 | 15 | 13 | 2 | 0 |
| **Total** | | **381** | **370** | **9** | **2** |

Rosenberg, Yang & Restifo
Nature Medicine
10, 909 - 915 (2004)

# Review of clinical vaccine studies worldwide in patients with metastatic cancer

| | Number of trials | Total | Objective responders | % |
|---|---|---|---|---|
| Published | | | | |
| | | (number of patients) | | |
| Peptide | 11 | 175 | 7 | 4.0% |
| Pox virus* | 8 | 258 | 1* | 0.4% |
| Tumor cells | 5 | 142 | 6 | 4.2% |
| Dendritic cells* | 10 | 198 | 14* | 7.1% |
| Heat shock proteins | 2 | 44 | 2 | 4.5% |
| Total | 34 | 765 | 29 | 3.9% |
| Surgery Branch | | | | |
| Peptide | 15 | 366 | 9 | 2.9% |
| Virus or DNA | 8 | 160 | 3 | 1.9% |
| Dendritic cells | 2 | 15 | 2 | 13.3% |
| Total | 25 | 541 | 14 | 2.6% |
| Overall: | 59 | 1366 | 43 | 3.3% |

**Headline news?** **14 objective responses to 541 vaccine cancer vaccine treatments in patients treated by our group since April, 1995 with 5 ongoing responses**

| Patient | Vaccine | Sites | Tumor size Before | After | Response (months) |
|---|---|---|---|---|---|
| 1 | MART-1 peptide | Mediastinal lymph node | 15.7 | 5.6 | 78 |
| 2 | MAGE-12 peptide | Neck lymph node | 6.0 | 0.4 | 29+ |
| 3 | Tyrosinase peptide | Mediastinal lymph node | 4.5 | 1.7 | 5 |
| 4 | TRP-2 peptide | Para-aortic lymph node | 3.6 | 0 | 27+ |
| | | lung | 0.12 | 0 | |
| 5 | gp100 (class I and II) & MART-1 peptide | Inguinal lymph node | 1.0 | 0 | 19 |
| 6 | NY-ESO-1 peptide | Mediastinal lymph node | 3.8 | 0.17 | 12 |
| | | subcutaneous | 0.73 | 0 | |
| 7 | gp100 peptide | Cutaneous/subcutaneous | 1.8 | 0 | 4 |
| 8 | Multiple peptides | Multiple cutaneous/subcutaneous | Small | | 3 |
| 9 | Multiple peptide immunizations | Lung | 5.9 | 0.60 | 4 |
| | | Liver | 3.2 | 0.48 | |
| | | Subcutaneous | 16.3 | 2.0 | |
| | | Intraperitoneal | 15.2 | 0 | |
| 10 | Adenovirus MART-1 | Mediastinal lymph node | 5.6 | 0 | 76+ |
| | | subcutaneous | 4.0 | 0 | |
| 11 | Mod Fowlpox-gp100 | Multiple cutaneous/subcutaneous | 55.4 | 0.1 | 50+ |
| 12 | gp100 DNA | Cutaneous | 0.1 | 0 | 50+ |
| 13 | Dendritic cells pulsed with peptide | Lung | 6.0 | 1.2 | 8 |
| | | Subcutaneous | 5.2 | 3.2 | |
| 14 | Dendritic cells pulsed with peptide | Cutaneous | 0.58 | 0.25 | 2 |

# Weighing the overall success of cancer vaccines on November 13th, 2005

- In mice, no significant treatment of any established unmanipulated tumors. Vaccine effects are only found when using artificial antigens (like allo-$L^d$, OVA, HA etc) and very small tumors.

- In man, ~2.6% of individuals with metastatic cancer may objectively respond to current cancer vaccine regimens with a durable objective response rate of <1%.

- Low objective response rates are consistent with those observed by workers worldwide.

*“Happy families are all alike; every unhappy family is unhappy in its own way.”*

The first line of *Anna Karenina,* by Leo Tolstoy *(1828 - 1910)*

The reasons for cancer vaccine failure to date are not fully understood:

- Perhaps each vaccine reported thus far may fail due to it’s own particular deficiencies.

- Alternatively, there may be overarching immunological mechanisms for vaccine failure.

In either case, intensive basic and translational research efforts are required for cancer vaccines to achieve success.

# The current state of cancer vaccines as 11/11/05

Stock Price

Trading volume



Stock Price

Trading volume



The solution: Make more efficacious cancer vaccines . . .

# Company press releases are now widely available due to the internet

- Press releases can lead to misinterpretation because they contain information that leads readers to incorrect conclusions not supported by the available data.
- Comments by physicians and scientists with affiliations to Universities and Research Institutes do not necessarily point out existing financial ties.
- Company press releases are often reported *verbatim* by the media as news leading physicians and patients to unsupported conclusions leading to the treatment of patients with medications that are costly and ineffective.
- The internet brings exposure for the field but also can bring unwanted sunshine to those with conflicts of interest.
- Misleading “hype” by a few can cause damage the field by causing mistrust by doctors and patients, as well as by funding and regulatory bodies.

# Separating “spin” from substance

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## BOX 1 CRITERIA FOR CLINICAL OBJECTIVE RESPONSE

**Conventional**

| | |
|---|---|
| Standard: | 50% decrease in the sum of the products of perpendicular diameters of all lesions: no increase in any lesion |
| RECIST: | 30% decrease in the sum of the largest diameters of target lesions; no increase in any lesion |

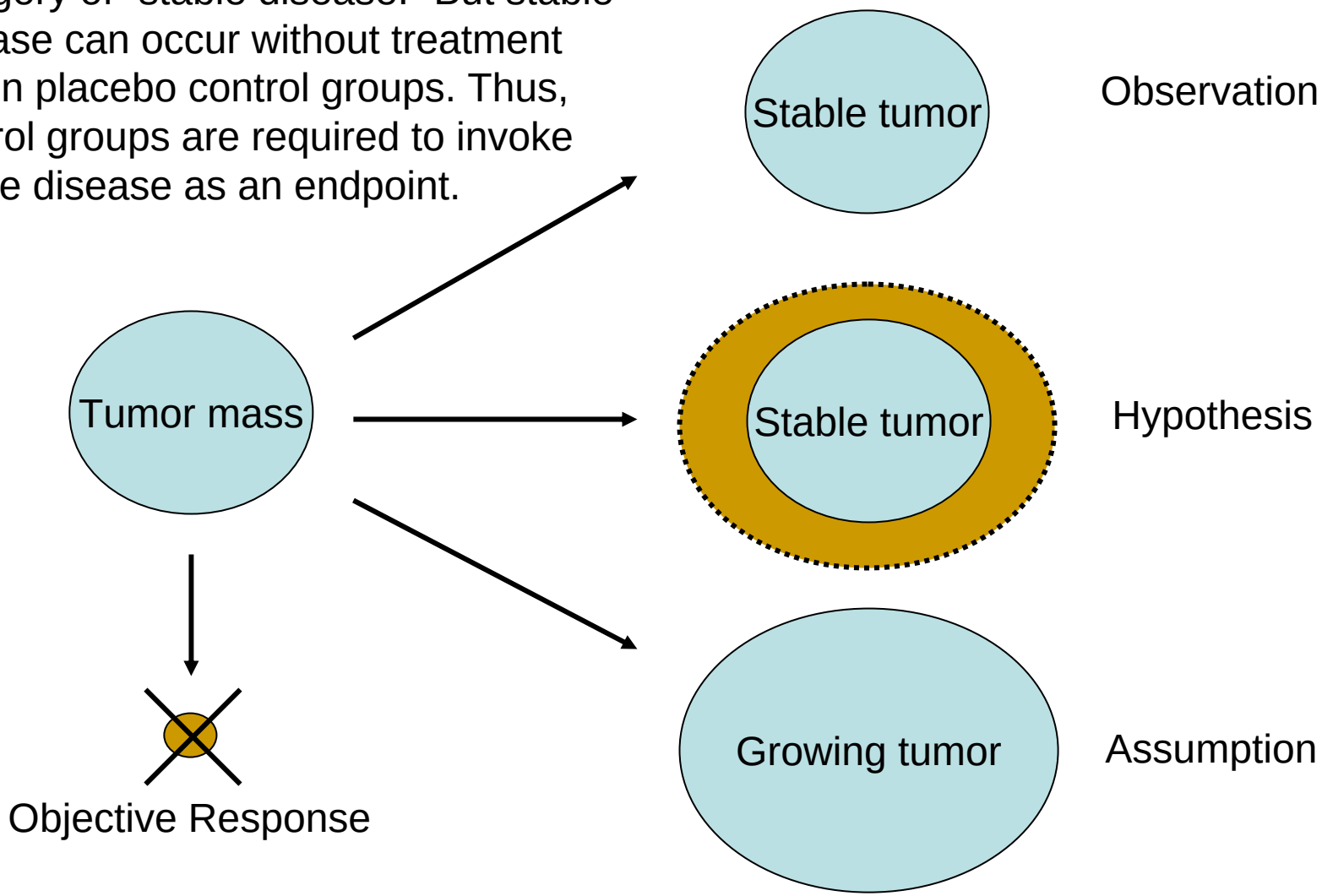
**Nonstandard criteria that lead to confusion (each of these ‘soft’ criteria can occur in the natural course of cancer growth):**

- “Tumor necrosis”
- “Lymphocyte infiltration”
- “Antigen loss”
- “Stable disease”
- “Shrinkage of some lesions”
- “Symptom improvement”
- “Survive longer than expected”

Rosenberg, Yang & Restifo, 2004

“Lowering the bar” for cancer vaccines has been proposed in a draft document of the Cancer Vaccine Clinical Trials Working Group

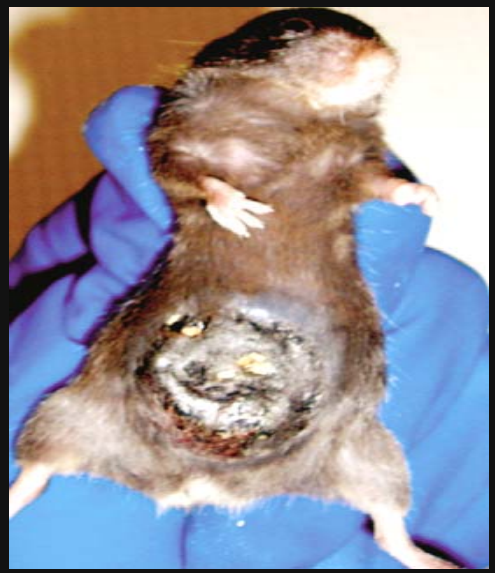

One proposal is to include a new category of “stable disease.” But stable disease can occur without treatment and in placebo control groups. Thus, control groups are required to invoke stable disease as an endpoint.

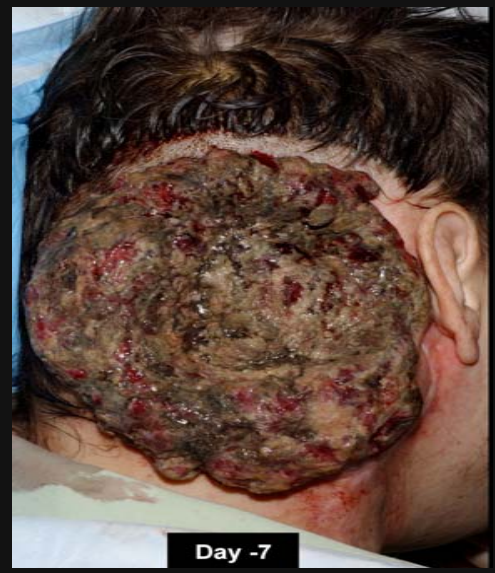


Clearly, radically new approaches
to cancer vaccines are required if we are to
optimally help our patients.

What can we learn from the current clinical and
preclinical data?

The challenge: Treat large (~1 cm) established, vascularized solid tumors in normal mice

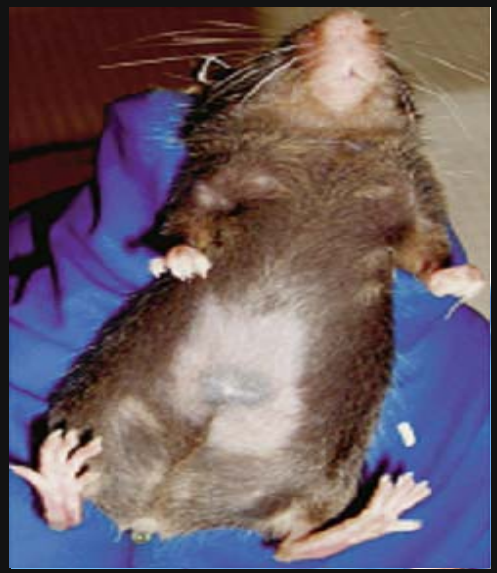


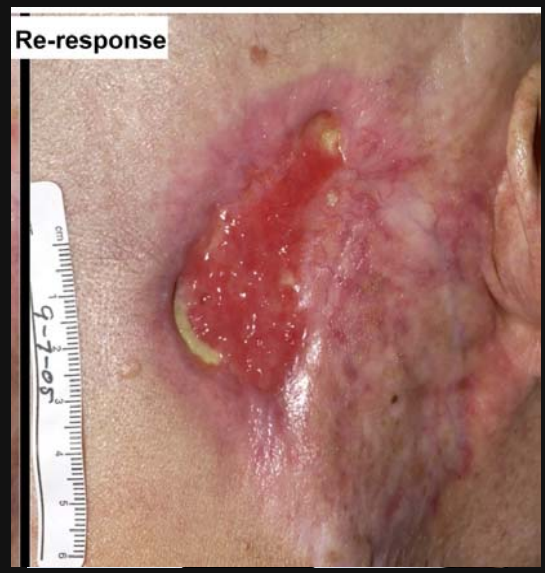



*The rules:*

Tumor must be unmanipulated; Treatment schema must be realistic

# The challenge: Treat large (~1 cm) established, vascularized solid tumors in normal mice

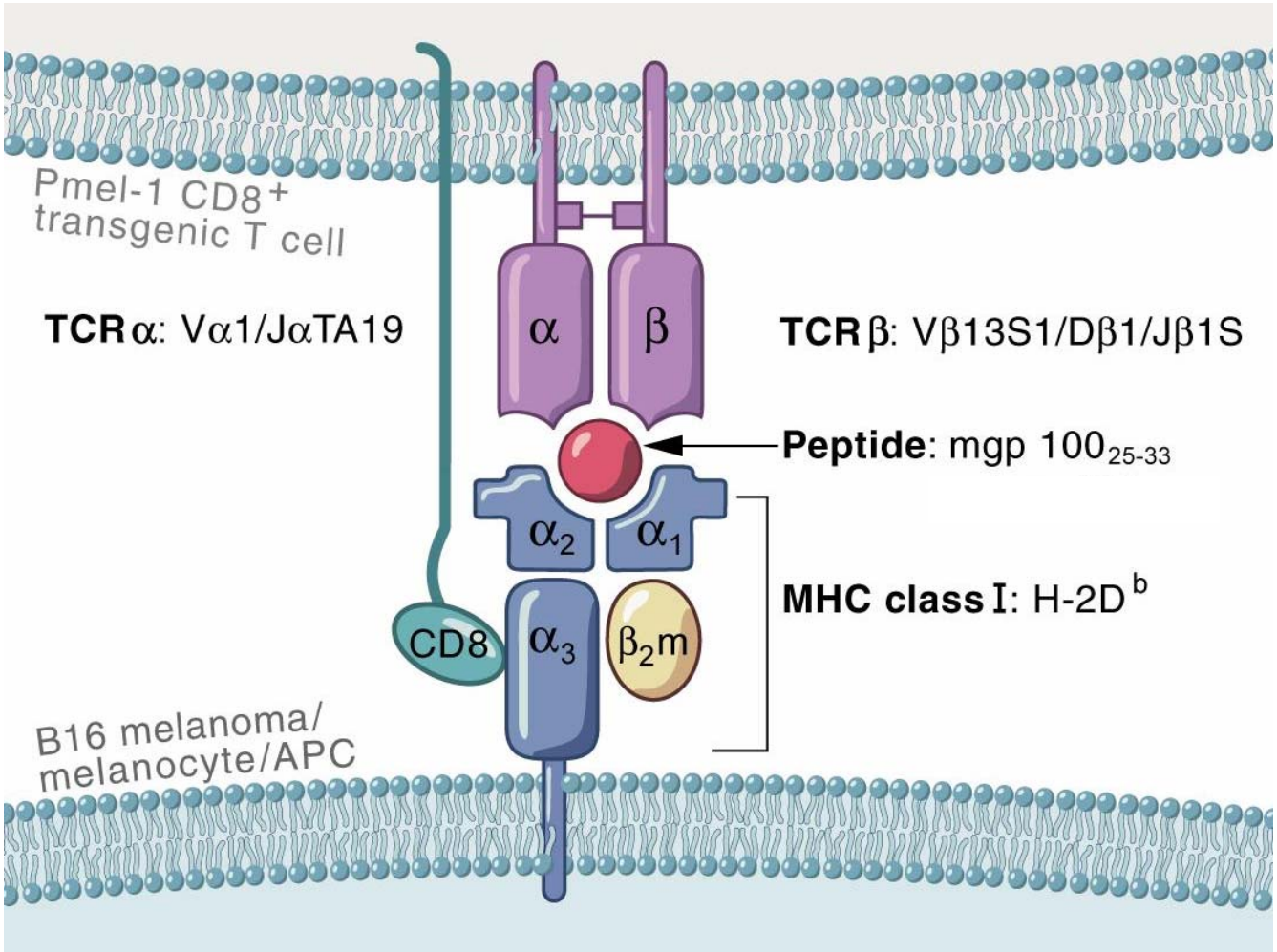





*The rules:*

Tumor must be unmanipulated; Treatment schema must be realistic

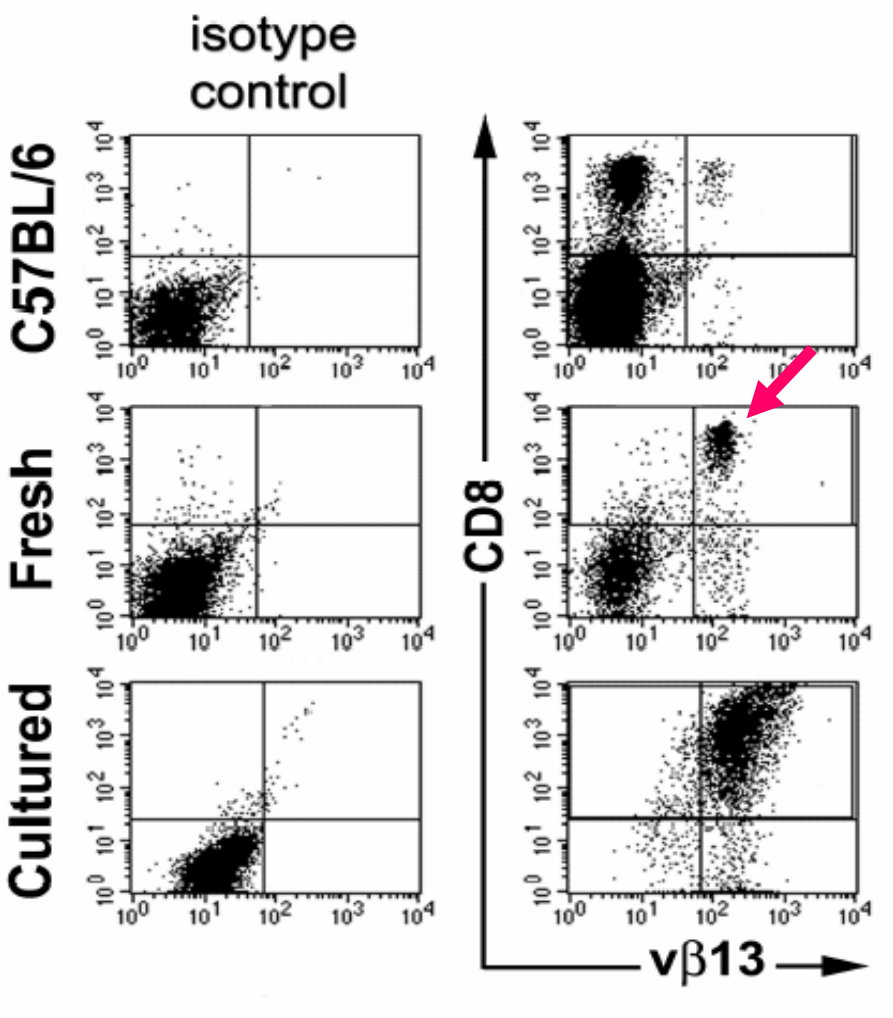
# An illustration of the pmel-1 TCR TG model




Overwijk, *J Exp Med*, 2003

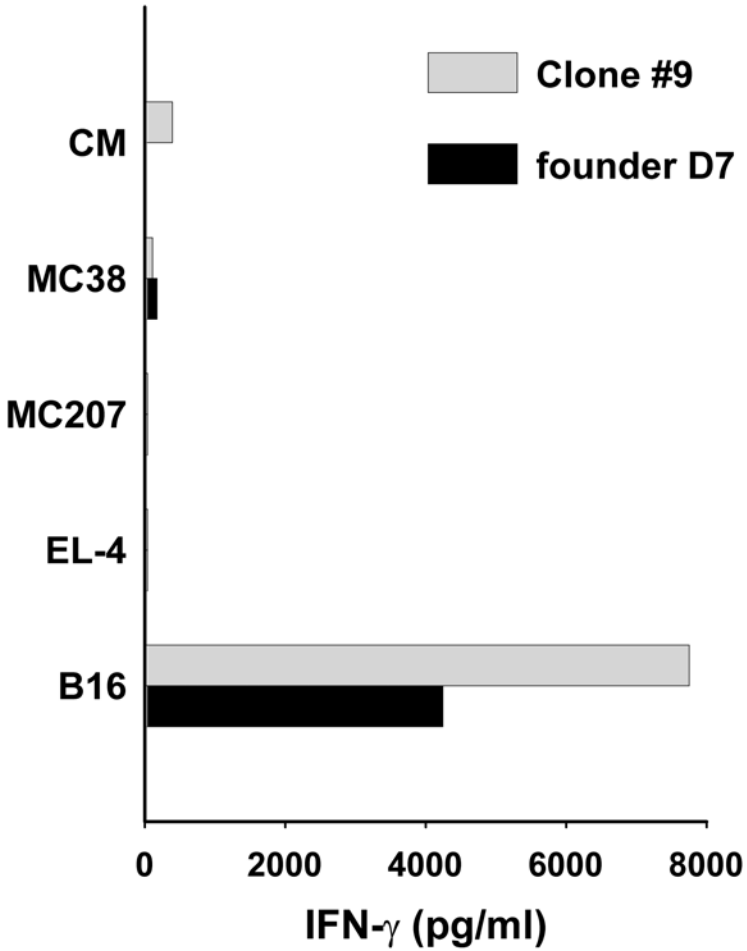
Pmel-1 mice are now available from www.jax.org

# Generation of pmel-1 transgenic mice: Phenotype

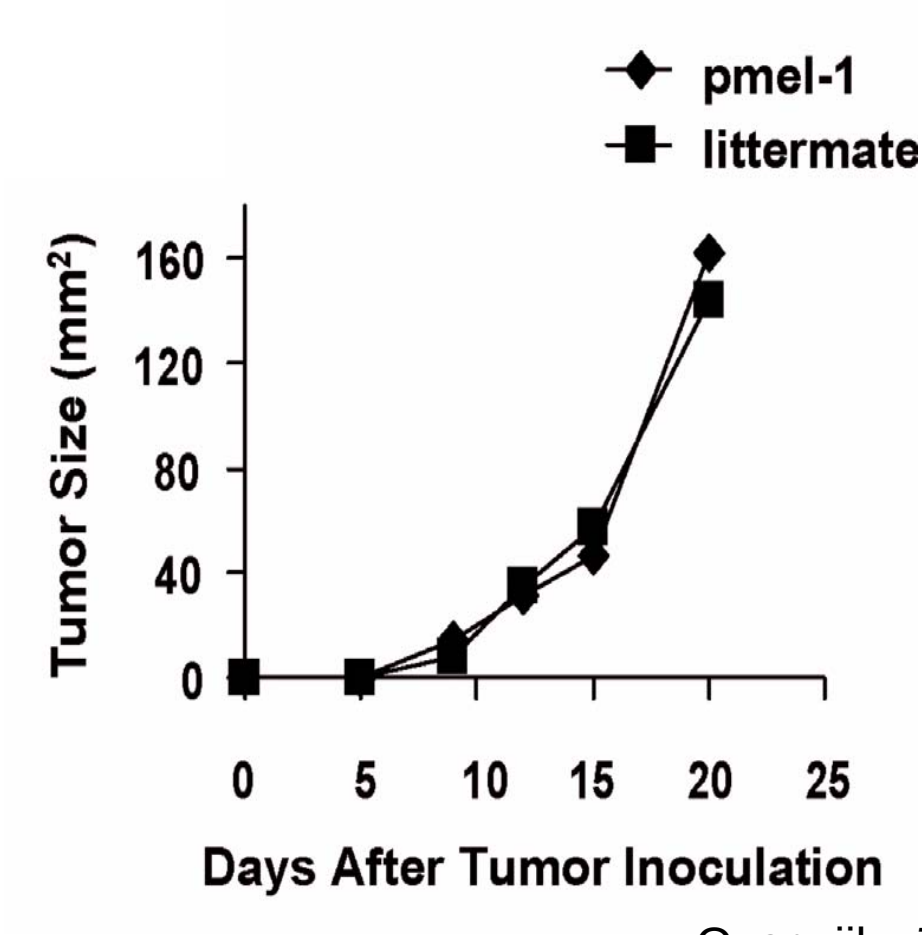



90-95% of all CD8+ T cells are transgenic

# Lymphocytes from pmel-1 TCR transgenic mice specifically recognize B16 tumor



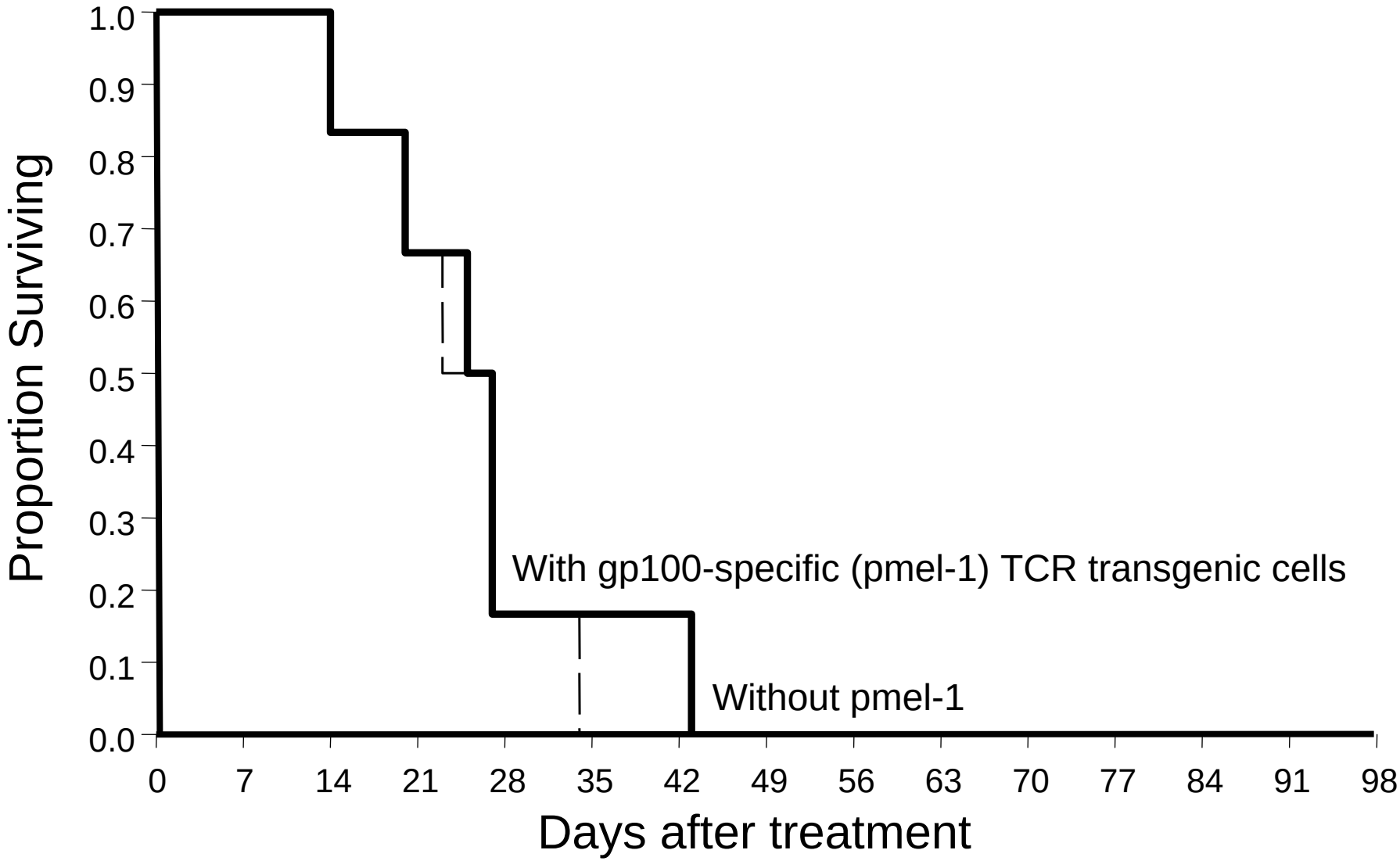
# The growth of B16 melanoma is unaltered in pmel-1 TCR transgenic mice




Overwijk, *J Exp Med*, 2003

# T cells aren't enough:

## Transgenic T cells do not alter the lethality of B16



# Questions to be asked in patients with cancer

- Can large numbers of tumor/self-reactive T cells be generated in patients?
- Do these anti-tumor T cells impact tumor growth?
- Are large tumor burdens limiting effectiveness?

Tumor progression can occur despite the induction of very high levels of self/tumor antigen-specific CD8+ T cells in patients with melanoma

*J Immunol*, Nov 1, 2005

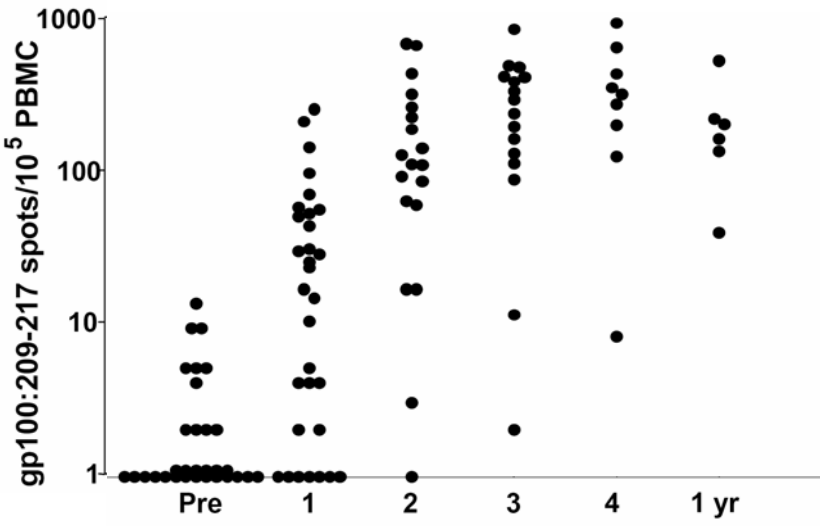
- Many tumor-associated epitopes are non-mutated “self” antigens, but non-tolerized self/tumor antigen-specific T cells can be found circulating.

- We repeatedly vaccinated 95 HLA-A*0201 patients with no measurable disease but who were at high risk for recurrence of malignant melanoma.

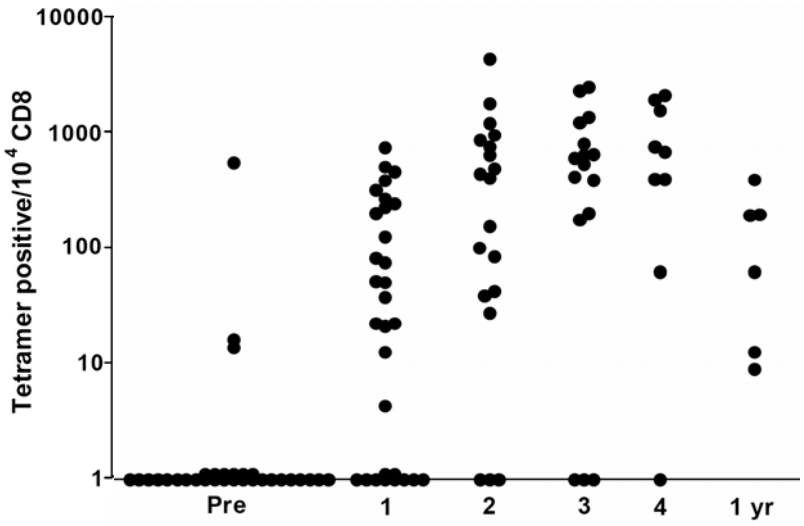
- Using an “anchor-modified” synthetic peptide, $gp100_{209\text{-}217(210M)}$, we induced large numbers of self/tumor-antigen reactive T cells in virtually every patient tested.

# Induction of large numbers of self/tumor-antigen reactive T cells using an “anchor-modified” synthetic peptide vaccine

ELISpot



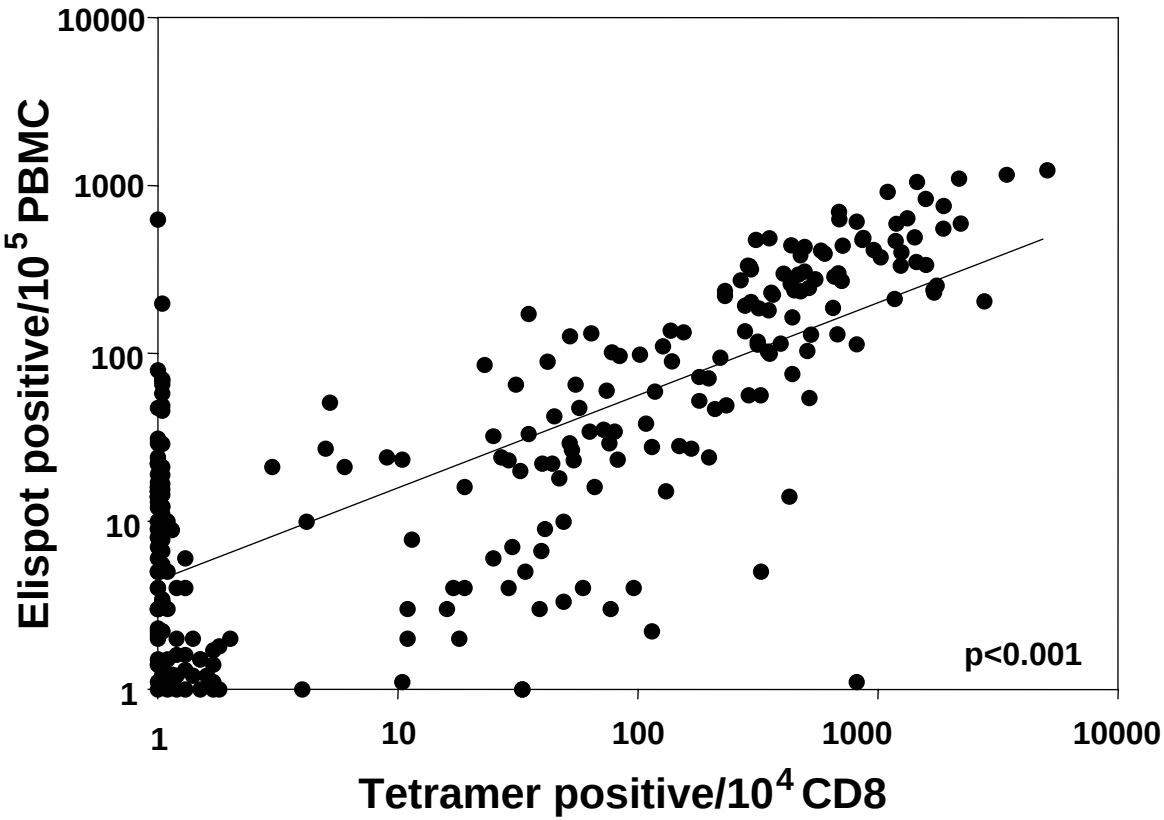

Tetramer




Patients were immunized repeated with the $gp100_{209\text{-}217(210M)}$ synthetic peptide

Rosenberg, et al, *J Immunol*, Nov 1, 2005

# Comparison of Elispot and Tetramer Assays on HLA-A*0201 Adjuvant Patients




*J Immunol*, Nov 1, 2005

# Conclusions

1. Large numbers of self/tumor-antigen reactive CD8+ T cells cells can be generated *in vivo* (as high 42% of CD8+ by tetramers).

> From 1 to 10% of all CD8+ cells were tumor-antigen reactive in 44% of patients and levels greater than 10% were generated in 17% of patients.

2. The mere presence of large numbers of vaccine-induced, self/tumor antigen-specific T cells cannot by themselves be used as a “surrogate marker” for vaccine efficacy.

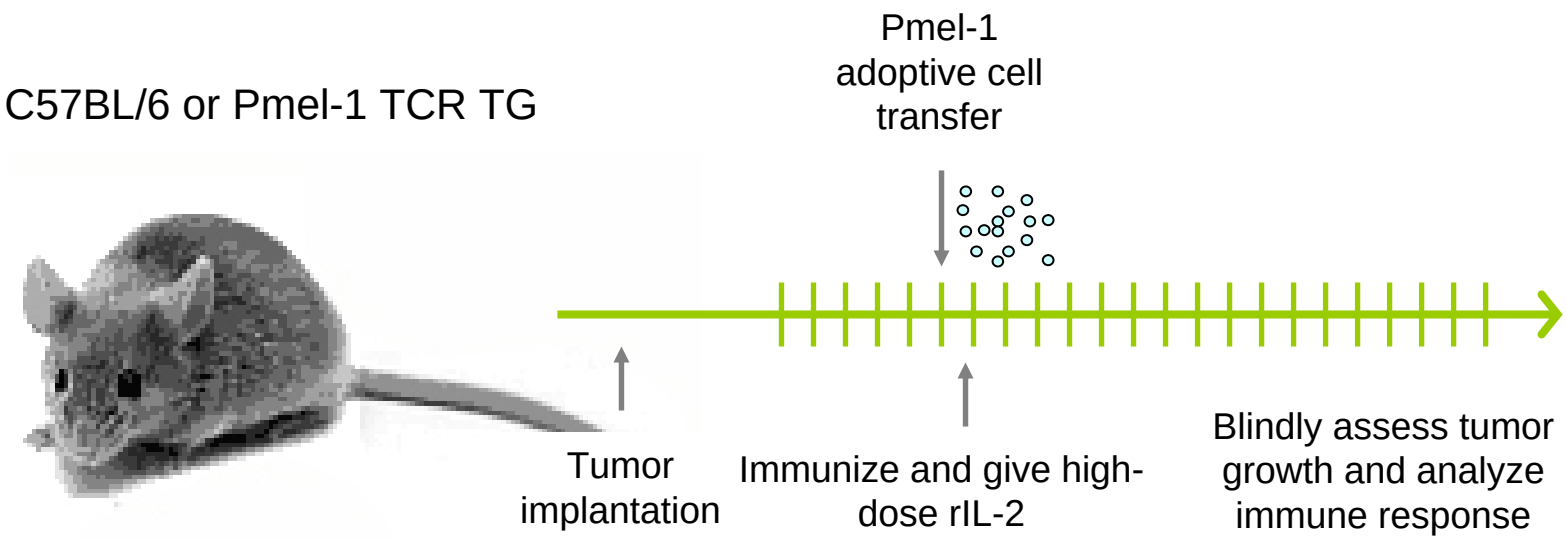
3. Antigen$^{+}$/MHC$^{+}$ tumors can recur in patients despite the presence of high levels of anti-tumor T cells.

4. There was no difference in the levels of anti-tumor antigen specific T cells in patients who recurred compared to those that remained disease free.

Recommend continued trials to test the efficacy of cancer vaccines in the adjuvant setting, including trials employing the modified $gp100_{209\text{-}217(210M)}$ synthetic peptide.

Rosenberg, et al, *J Immunol*, Nov 1, 2005

# Are the current tumor vaccines useless?




A tripartite regimen is effective:

i) immunization

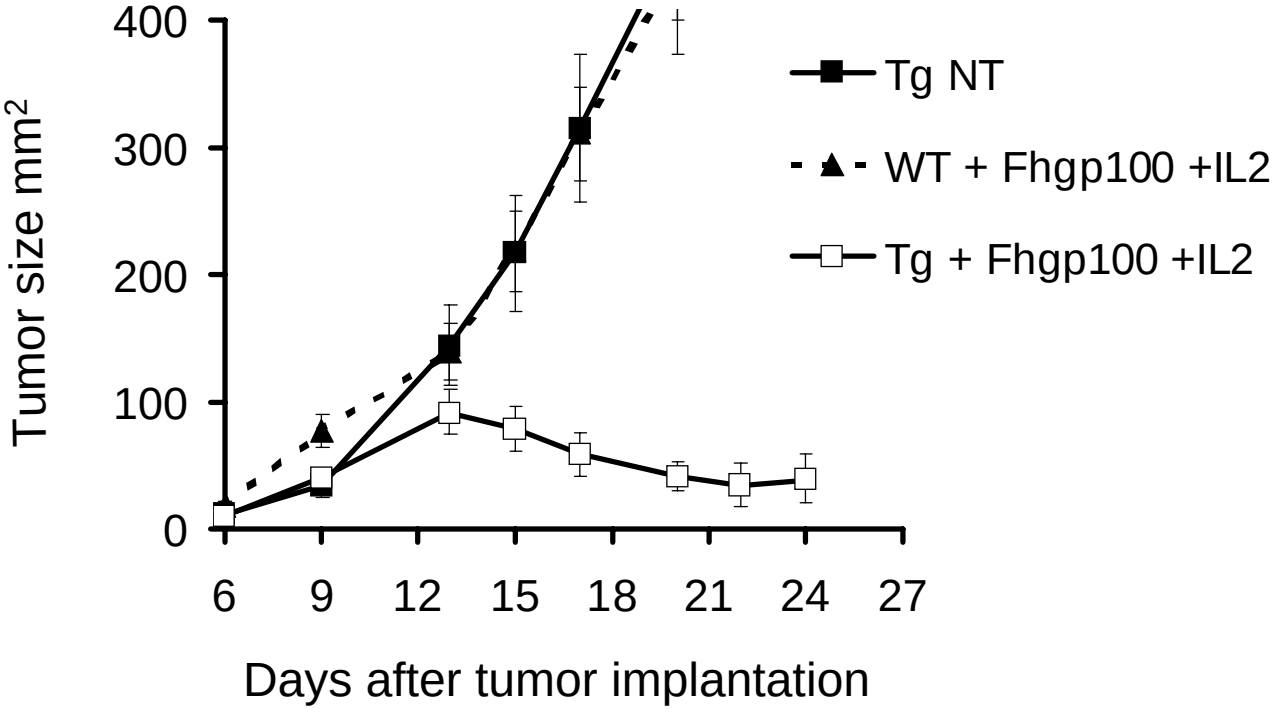
ii) adoptive transfer of anti-tumor T cells

iii) administration of high-dose IL-2

(Overwijk, JEM, 2003)

Note that other **(**$_C$ cytokines are also effective in this model including IL-21 (Zeng, J Exp Med, 2005), IL-15 (Klebanoff, PNAS, 2004) and IL-7 (unpublished)

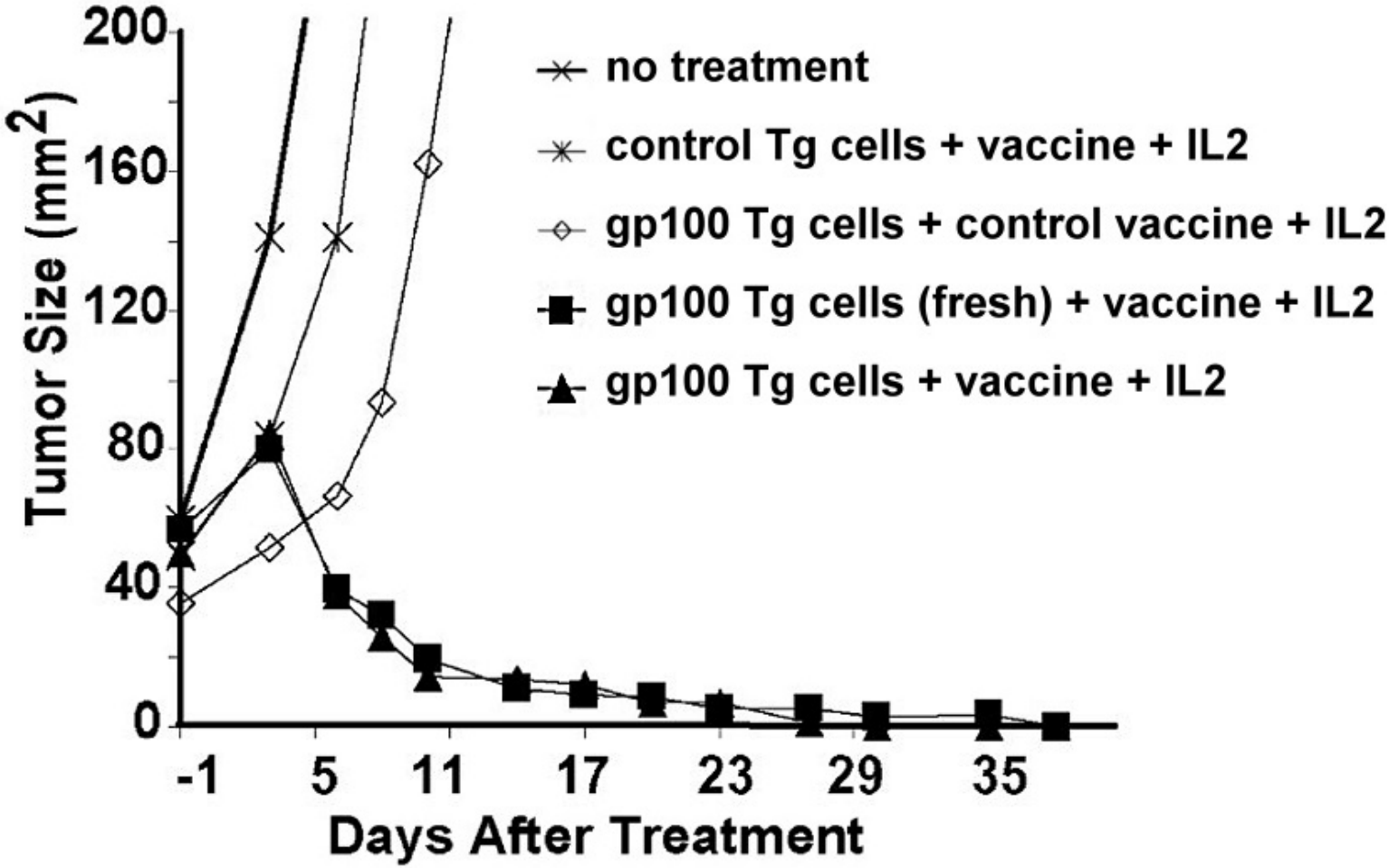
# Neither transgenic T cells alone nor vaccination alone are sufficient to induce the regression of B16



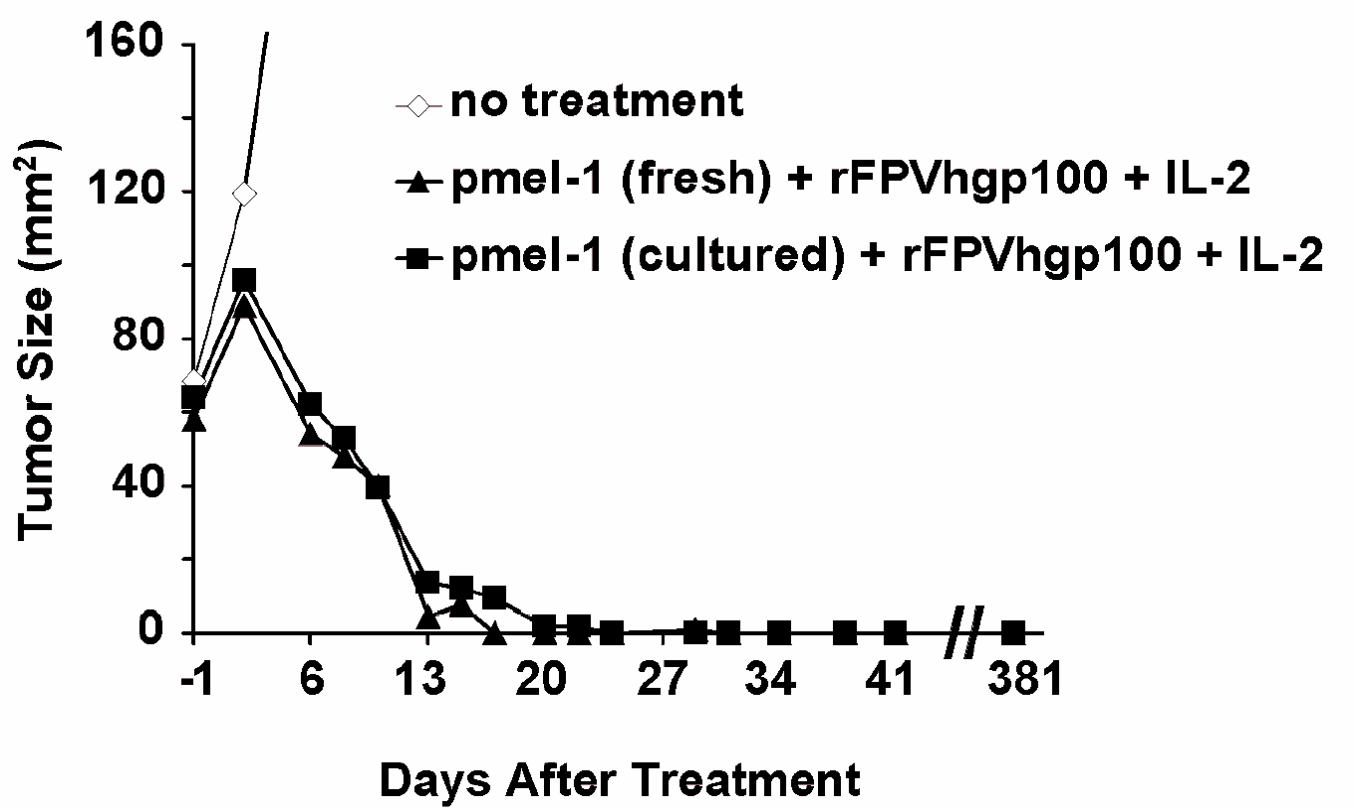

Treatments started in normal C57BL/6 mice 11 days after tumor implantation

Palmer, *J Immunol*, 2004

# Transgenic T-Cells Expressing the TCR for gp100 Can Treat B16 Tumor



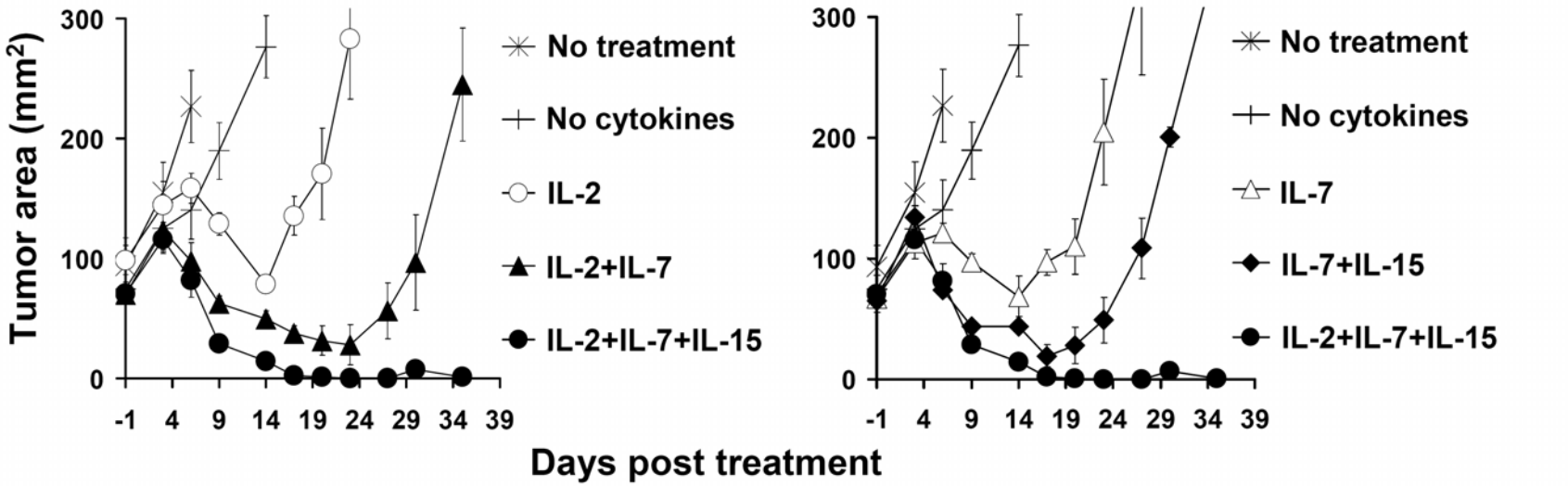
Using the optimal vaccine regimen with adoptive cell transfer and IL-2, very large (~ 1 cm in diameter), established B16 melanomas can be cured



# Autoimmune vitiligo is observed in mice treated with pmel-1-based immunotherapy

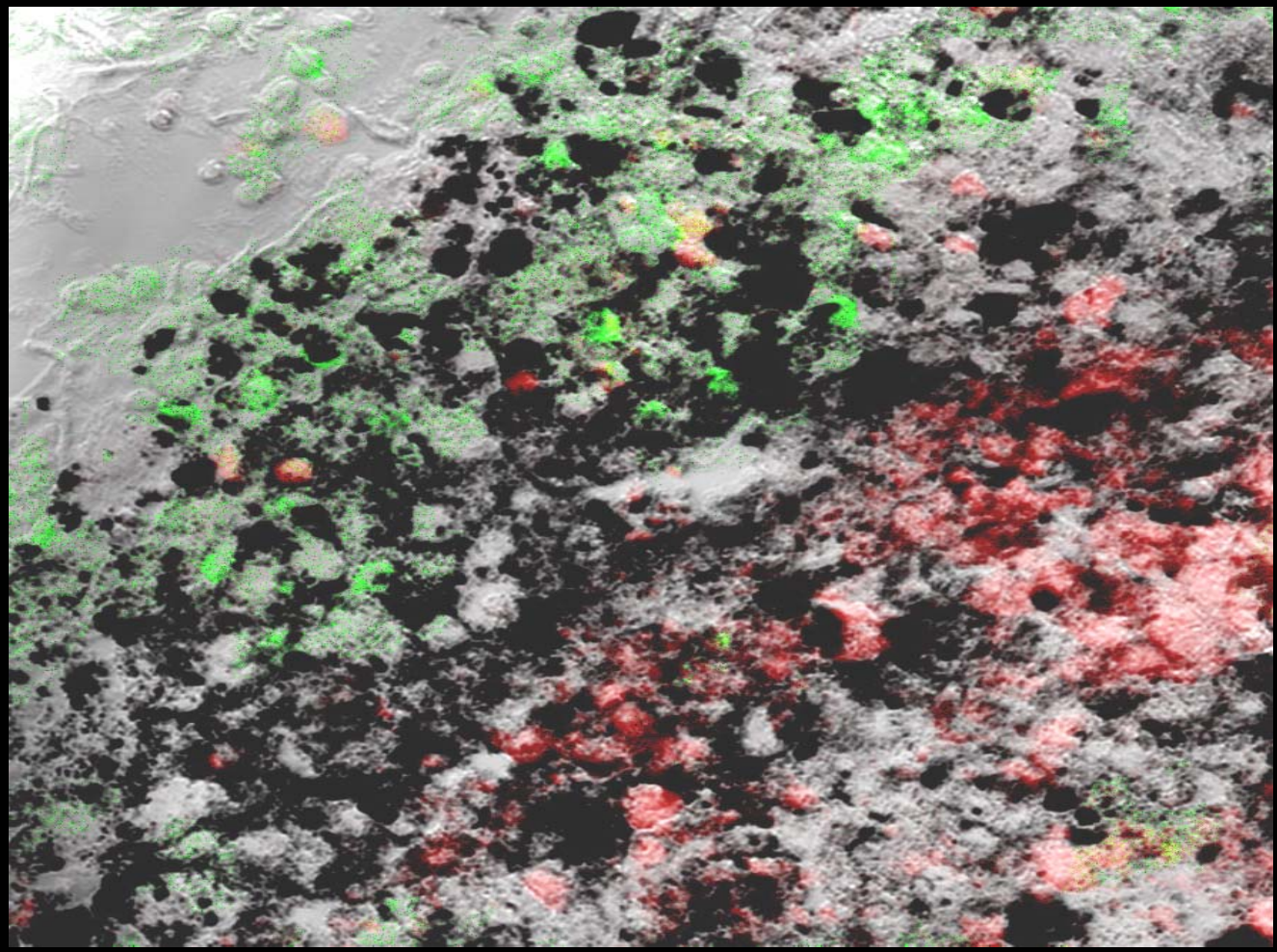
Overwijk, J Exp Med, 2003

# Combinations of IL-2, IL-7 and IL-15 dramatically improved the anti-tumor regimen using limiting numbers of transferred cells



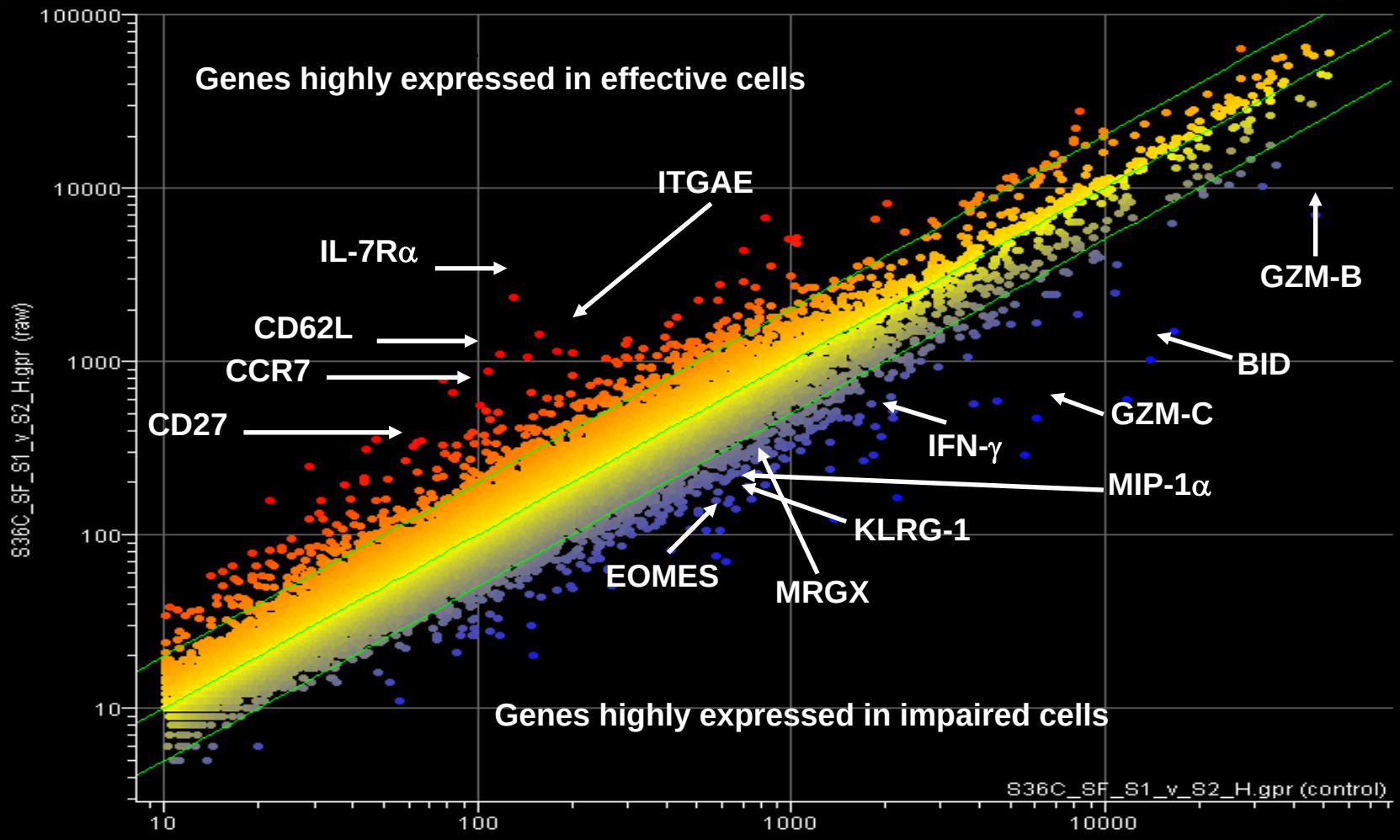

TBI WT mice bearing 12-day-old established subcutaneous B16 tumors were left untreated as control or received adoptive transfer of 1 x 106 cultured pmel-1 T cells in conjunction with rFPhgp100 vaccination alone or with indicated combination of exogenous cytokines (36mg per dose of IL-2 and IL-15,10mg per dose of IL-7).

# The battle front: How anti-tumor T cells (green) attack and kill tumor cells (red) *in vivo*



Vb13 (green), active caspase 3 (red) in B16, 5 days after treatment

# Further characterization of effective and impaired T cells




Gattinoni, J Clin Investig, In Press, 2005

## Conclusions

• The current cancer vaccines used alone do not reliably induce the regression of established tumors in mouse or in man.

• Large numbers of tumor-specific T cells capable of recognizing tumor cells *ex vivo* remain quiescent *in vivo* and do not affect tumor growth or lethality.

• T cells can be activated *in vivo* with vaccination and **(**$_C$ cytokines and with lymphodepletion.

• The current cancer vaccines can result in the treatment of large, established tumors when used in combination with adoptively transferred anti-tumor T cells.

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Dan Powell
Keith Kerstann
Mark Theoret

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Pat Hwu
Willem Overwijk