

Society for Immunotherapy of Cancer (SITC)

Active Immunization Approaches

David Bartlett, MD – *University of Pittsburgh*

Advances in Cancer Immunotherapy™ - Pennsylvania
July 31, 2015

Presentation originally prepared and presented by
Willem W. Overwijk, PhD
MD Anderson Cancer Center
Houston, TX, USA



Society for Immunotherapy of Cancer

Disclosures

What is a Cancer Vaccine?

A preparation of a tumor antigen (usually protein) that upon administration stimulates tumor-specific antibodies and/or T cells

When could cancer vaccines be useful?

- **Cancer Prevention**
- **Cancer therapy**

When could cancer vaccines be useful?

- Cancer Prevention
- **Cancer therapy**

Clinical Trials of Cancer Vaccines

402 open studies (USA only) using cancer vaccines (www.clinicaltrial.gov)

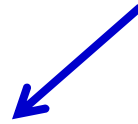
1. Study of Peptide Vaccination With Tumor Associated Antigens Mixed With Montanide in Patients With **CNS Tumors**
2. CpG 7909/IFA With or Without Cyclophosphamide in Combination Either With NY-ESO-1-derived Peptides or the NY-ESO-1 Protein for **NY-ESO-1-expressing Tumors**
3. Vaccine Therapy in Treating Patients With **Non-Small Cell Lung Cancer** (NSCLC) Stages IIIB/IV
4. Randomized Study of Adjuvant WT-1 Analog Peptide Vaccine in Patients With Malignant Pleural **Mesothelioma** (MPM) After Completion of Combined Modality Therapy
5. Immunotherapy of Stage III/IV **Melanoma** Patients
6. A Clinical Trial of Autologous Oxidized Tumor Cell Lysate Vaccine For Recurrent **Ovarian, Fallopian Tube or Primary Peritoneal Cancer**
7. Vaccine Therapy and Monoclonal Antibody Therapy in Treating Patients With Stage III or Stage IV **Melanoma** That Cannot Be Removed by Surgery
8. Safety Study of Multiple-Vaccine to Treat **Metastatic Breast Cancer**
9. IDO Peptide Vaccination for Stage III-IV **Non Small-cell Lung Cancer** Patients.
10. Survivin Vaccine Therapy for Patients With **Malignant Gliomas**
11. Phase I Poly IC:LC and NY-ESO-1/gp100/MART (**Melanoma**)
12. A Phase I Study of WT1 Peptides to Induce Anti-Leukemia Immune Responses Following Autologous or Allogeneic Transplantation for **AML, CML, ALL, MDS, and B Cell Malignancies**
13. Vaccination of High Risk **Breast Cancer** Patients
14. MAGE-A3/HPV 16 Vaccine for **Squamous Cell Carcinoma of the Head and Neck**
15. Novel Adjuvants for Peptide-Based **Melanoma** Vaccines

What is a Cancer Vaccine?

A **preparation** of a **tumor antigen** (usually protein) that upon administration stimulates tumor-specific antibodies and/or T cells

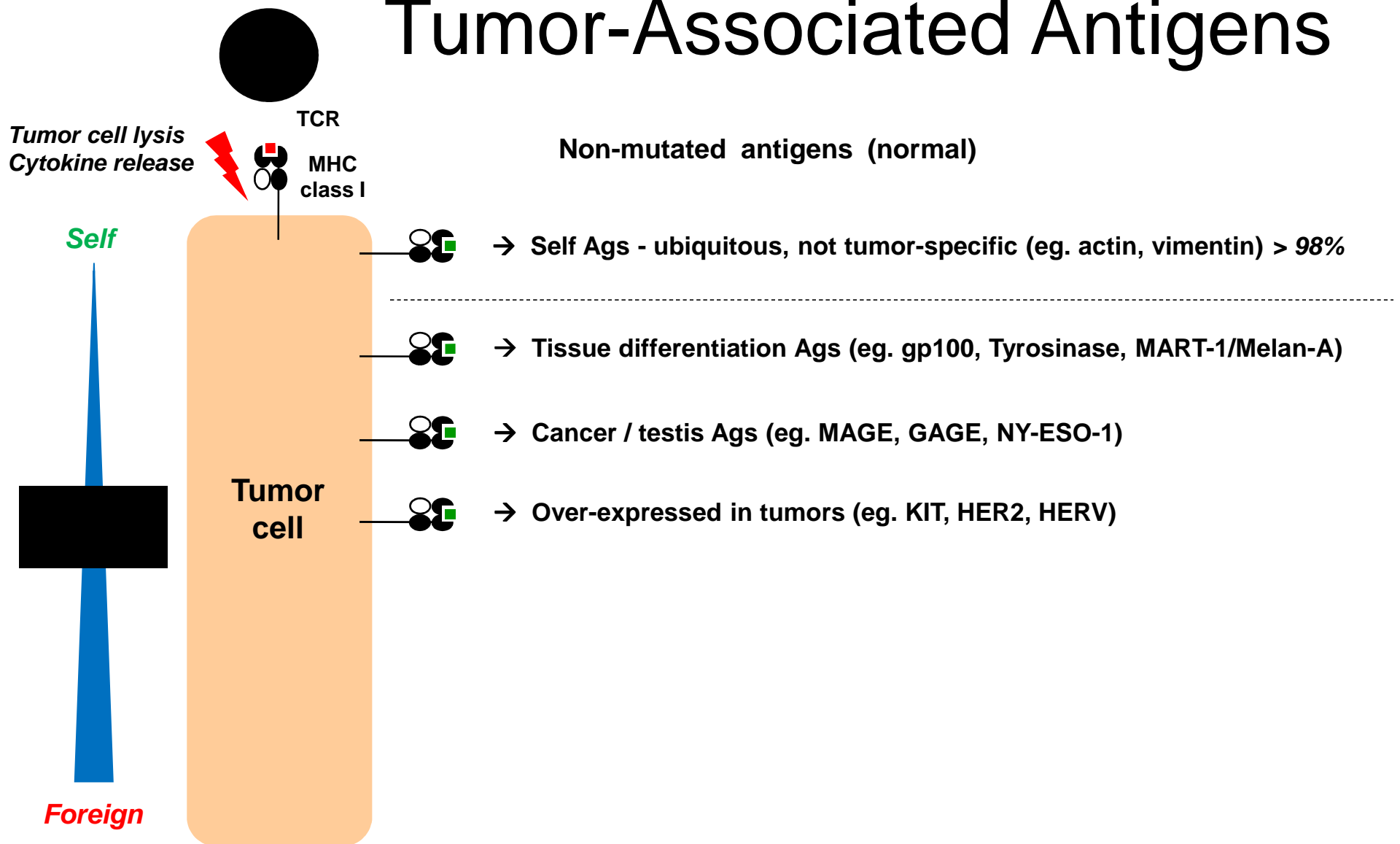
What is a Cancer Vaccine?

peptide(s)

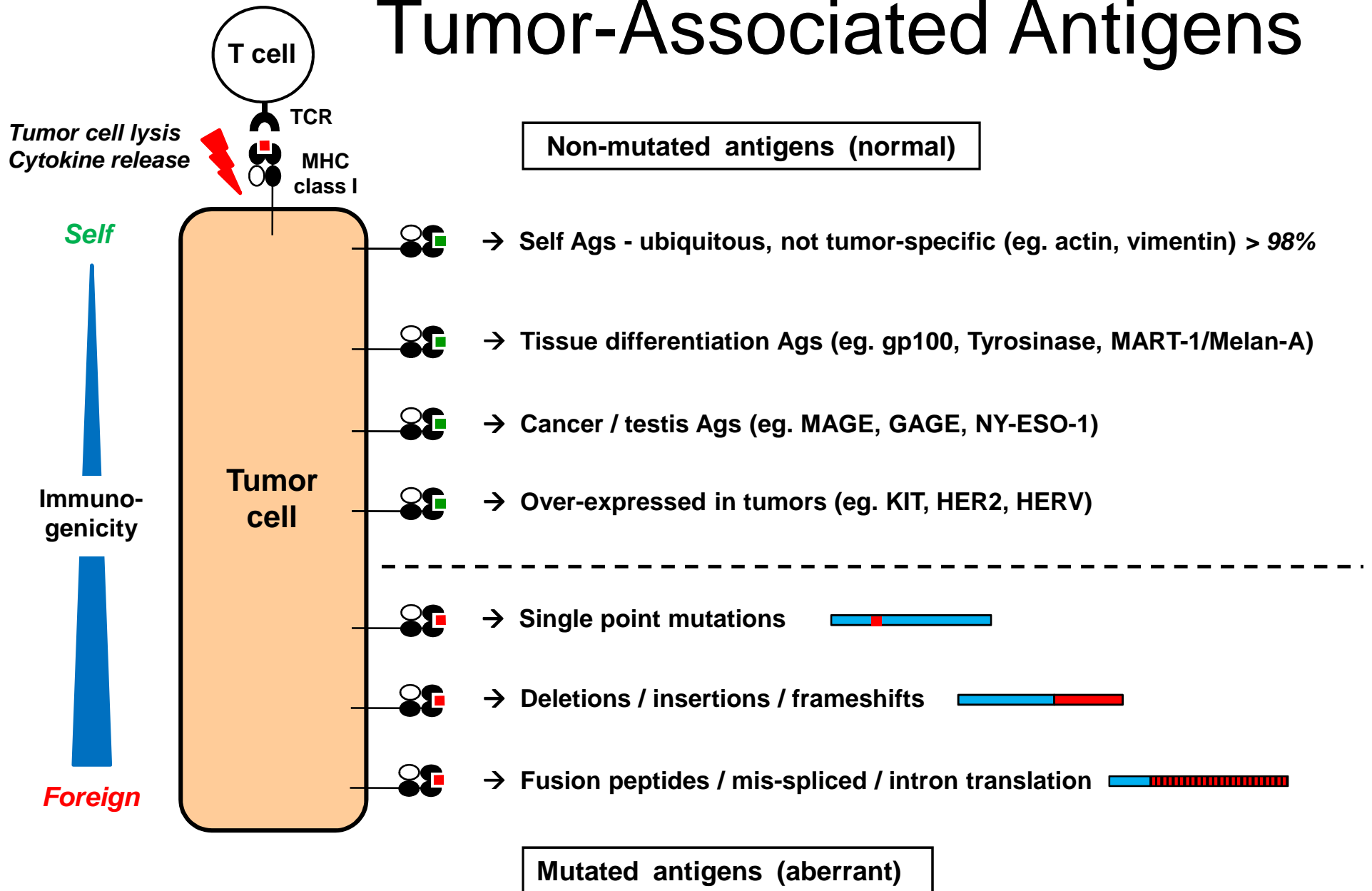


A **preparation** of a **tumor antigen** (usually protein) that upon administration stimulates tumor-specific antibodies and/or T cells

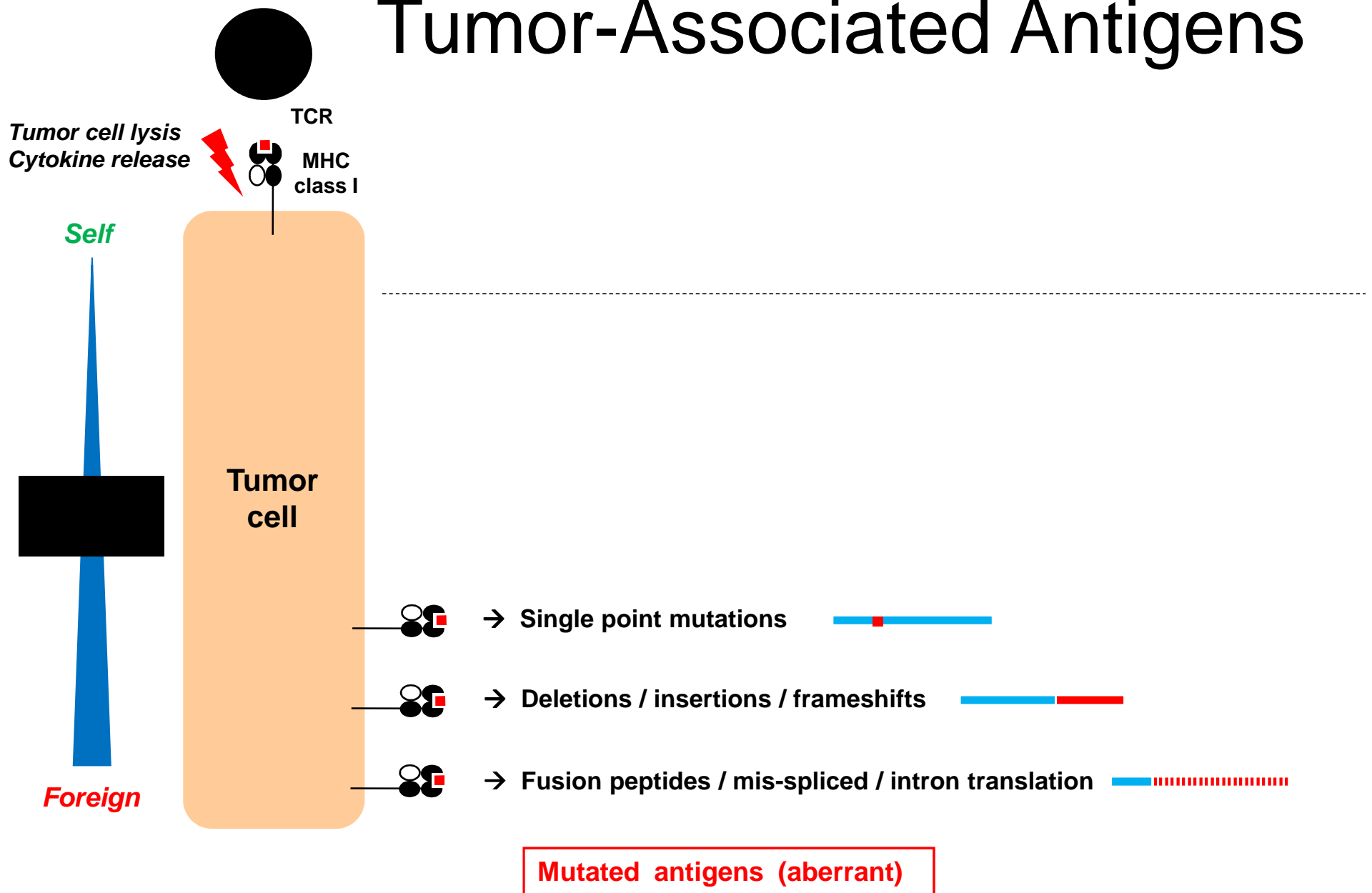
Tumor-Associated Antigens



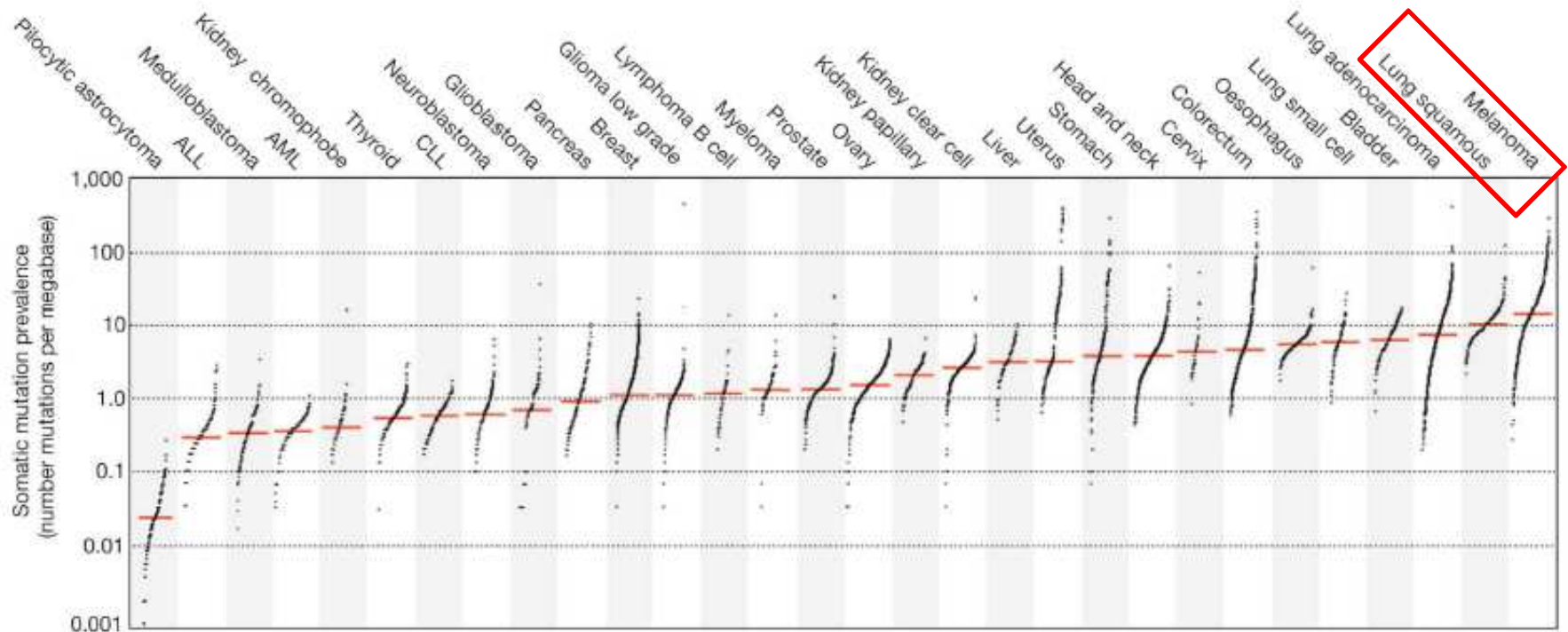
Tumor-Associated Antigens



Tumor-Associated Antigens



The prevalence of somatic mutations across human cancer types



Signatures of mutational processes in human cancer Alexandrov et al.

Nature Volume: 500, Pages: 415–421 Date published: (22 August 2013) DOI: doi:10.1038/nature12477

The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

Genetic Basis for Clinical Response to CTLA-4 Blockade in Melanoma

Alexandra Snyder, M.D., Vladimir Makarov, M.D., Taha Merghoub, Ph.D.,
Jianda Yuan, M.D., Ph.D., Jesse M. Zaretsky, B.S., Alexis Desrichard, Ph.D.,
Logan A. Walsh, Ph.D., Michael A. Postow, M.D., Phillip Wong, Ph.D.,
Teresa S. Ho, B.S., Travis J. Hollmann, M.D., Ph.D., Cameron Bruggeman, M.A.,
Kasthuri Kannan, Ph.D., Yanyun Li, M.D., Ph.D., Ceyhan Elipenahli, B.S.,
Cailian Liu, M.D., Christopher T. Harbison, Ph.D., Lisu Wang, M.D.,
Antoni Ribas, M.D., Ph.D., Jedd D. Wolchok, M.D., Ph.D.,
and Timothy A. Chan, M.D., Ph.D.

Anti-CTLA-4 in cutaneous melanoma



B Survival in Discovery Set

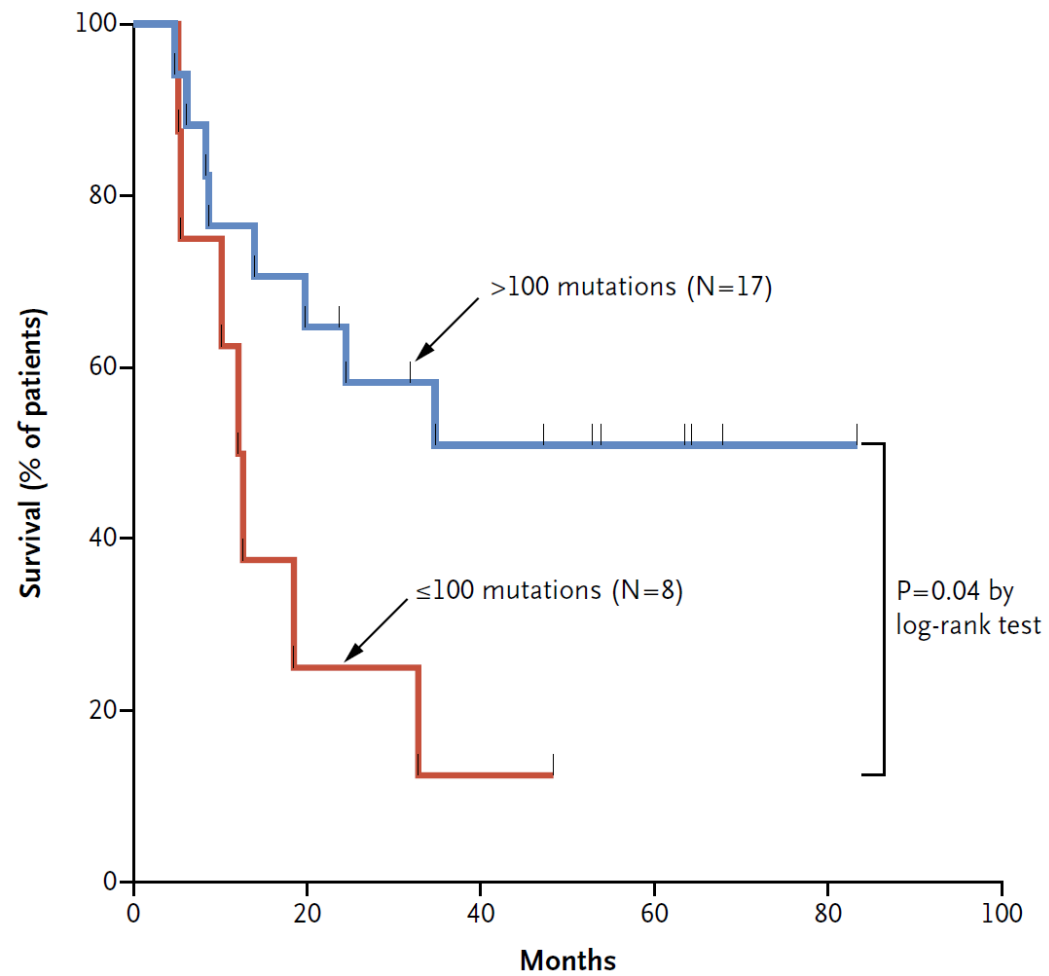
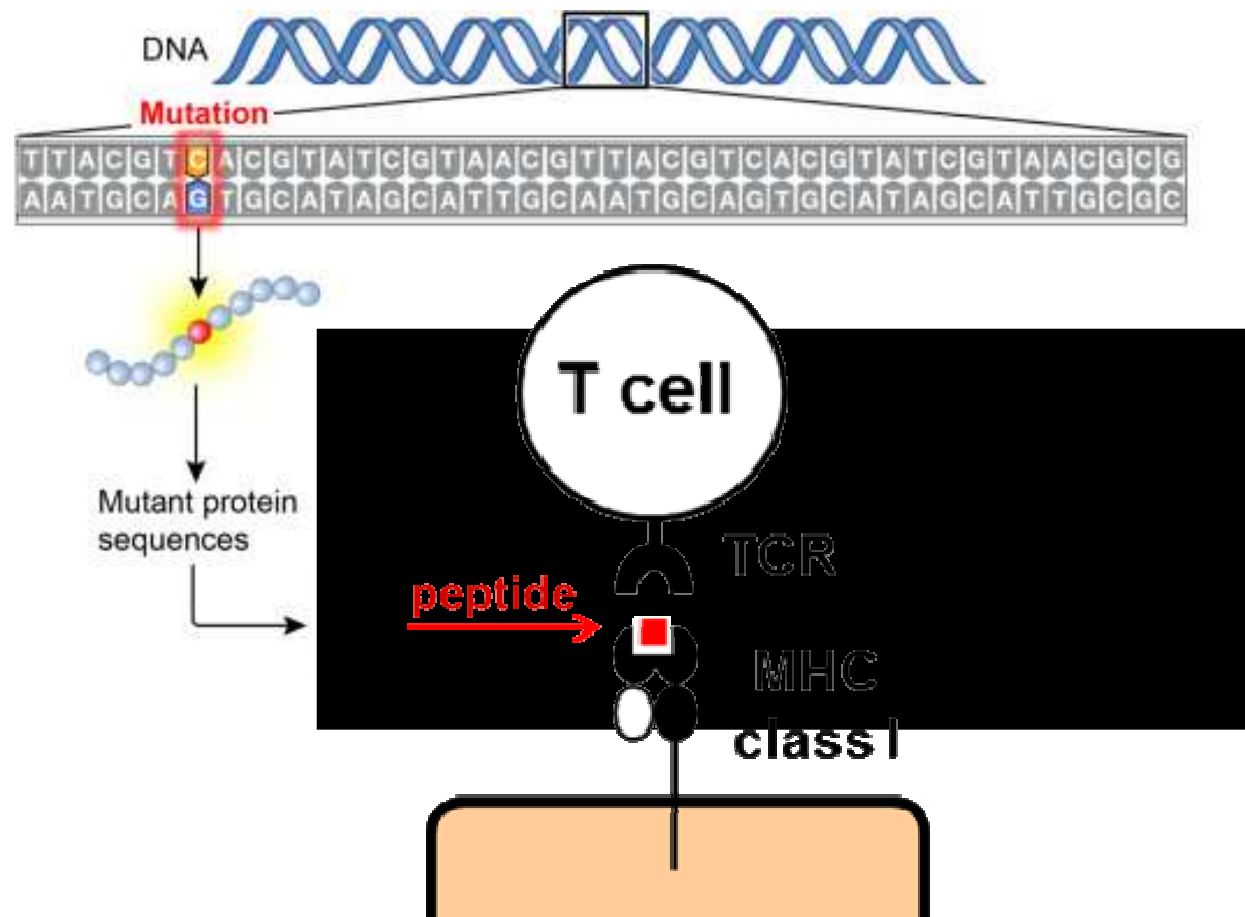
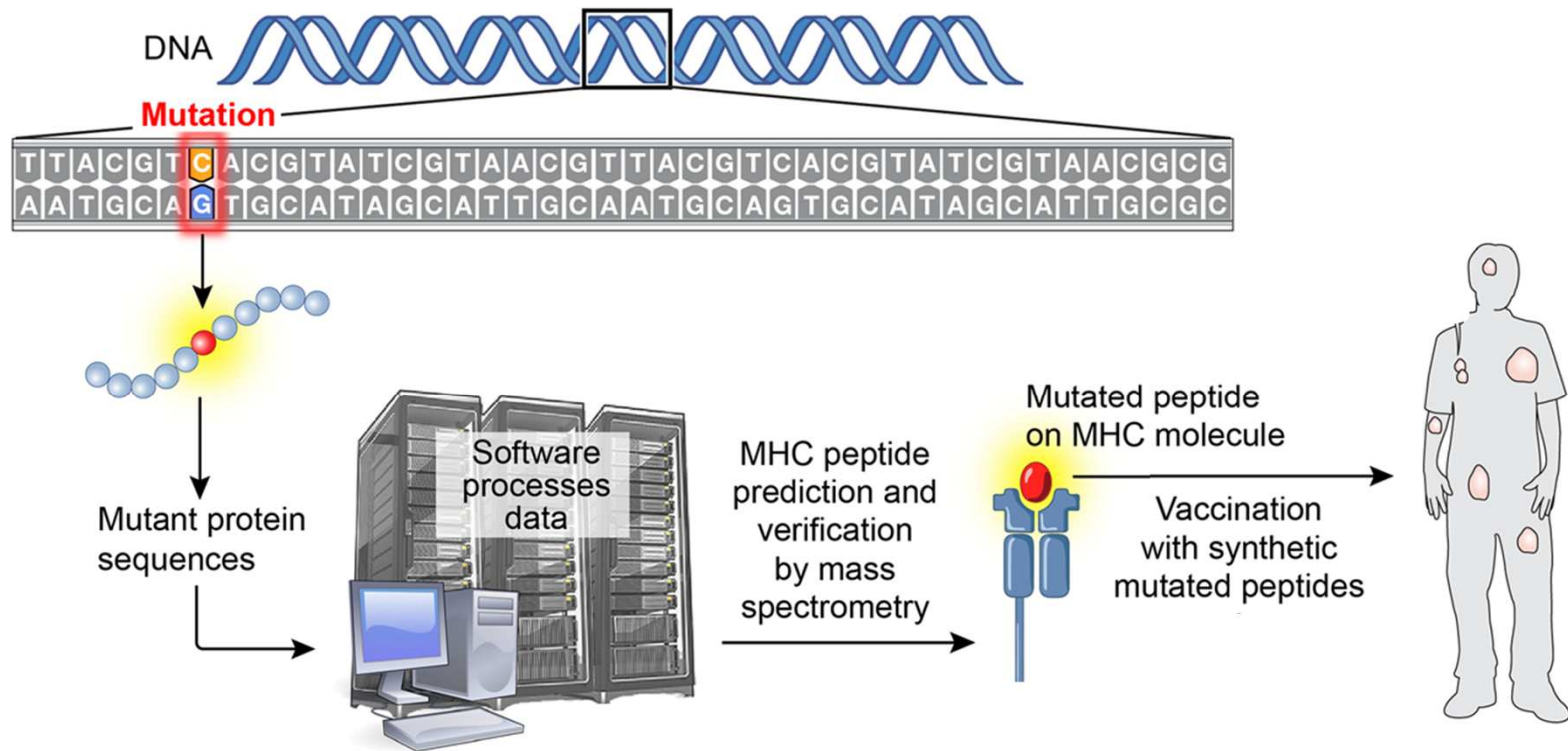


Figure 2. Mutational Landscape of Tumors According to Clinical Benefit from Ipilimumab Treatment.

Mutated Peptides as Cancer Antigens



From Mutation to Vaccine



What is a Cancer Vaccine?

vaccine adjuvant



A **preparation** of a **tumor antigen** (usually protein) that upon administration stimulates tumor-specific antibodies and/or T cells

Vaccine Adjuvants

- mechanisms of action:
 - antigen depot for prolonged release
 - protects antigen from degradation
 - increases antigen uptake by APCs
 - pro-inflammatory/pro-immunogenic milieu

ORIGINAL ARTICLE

gp100 Peptide Vaccine and Interleukin-2 in Patients with Advanced Melanoma

Douglas J. Schwartzentruber, M.D., David H. Lawson, M.D.,
Jon M. Richards, M.D., Ph.D., Robert M. Conry, M.D.,
Donald M. Miller, M.D., Ph.D., Jonathan Treisman, M.D., Fawaz Gailani, M.D.,
Lee Riley, M.D., Ph.D., Kevin Conlon, M.D., Barbara Pockaj, M.D.,
Kari L. Kendra, M.D., Ph.D., Richard L. White, M.D., Rene Gonzalez, M.D.,
Timothy M. Kuzel, M.D., Brendan Curti, M.D., Phillip D. Leming, M.D.,
Eric D. Whitman, M.D., Jai Balkissoon, M.D., Douglas S. Reintgen, M.D.,
Howard Kaufman, M.D., Francesco M. Marincola, M.D., Maria J. Merino, M.D.,
Steven A. Rosenberg, M.D., Ph.D., Peter Choyke, M.D., Don Vena, B.S.,
and Patrick Hwu, M.D.

gp100 peptide vaccine has activity in metastatic melanoma

Stage IV and locally advanced stage III melanoma patients

High-dose IL-2 +/- gp100 peptide in IFA (= water-in-oil emulsion)

	IL-2+gp100/IFA	IL-2	p-value
Overall response rate	22.1%	9.7%	0.022
Progression free survival	2.9 months	1.6 months	0.010
Median overall survival	17.6 months	12.8 months	0.096

Peptide-based Cancer Vaccines

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Vaccination against HPV-16 Oncoproteins for Vulvar Intraepithelial Neoplasia

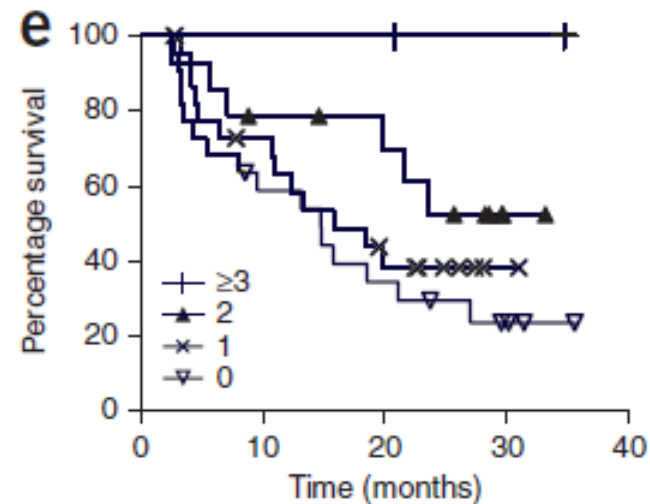
Gemma G. Kenter, M.D., Ph.D., Marij J.P. Welters, Ph.D.,
A. Rob P.M. Valentijn, Ph.D., Margriet J.G. Lowik,
Dorien M.A. Berends-van der Meer, Annelies P.G. Vloon, Farah Essahsah,
Lorraine M. Fathery, Rienk Offringa, Ph.D., Jan Wouter Drijfhout, Ph.D.,
Amon R. Wafelman, Ph.D., Jaap Oostendorp, Ph.D., Gert Jan Fleuren, M.D., Ph.D.,
Sjoerd H. van der Burg, Ph.D., and Cornelis J.M. Melief, M.D., Ph.D.

79% clinical response
47% CR (>24 months)

Immune response can correlate with clinical outcome

**nature
medicine**

AUGUST 2012

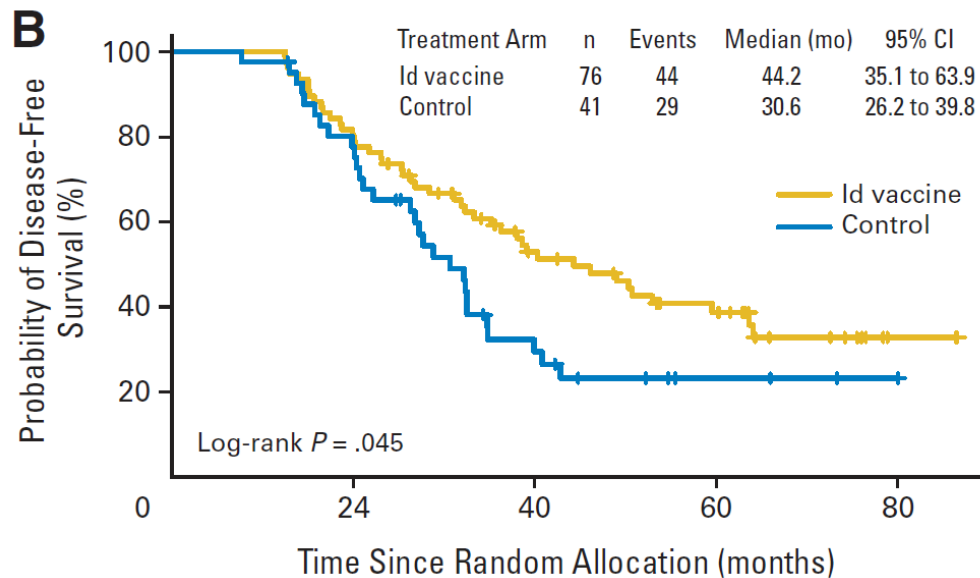


Multipeptide immune response to cancer vaccine IMA901 after single-dose cyclophosphamide associates with longer patient survival

Steffen Walter^{1,21}, Toni Weinschenk^{1,21}, Arnulf Stenzl², Romuald Zdrojowy³, Anna Pluzanska⁴, Cezary Szczylik⁵, Michael Staehler⁶, Wolfram Brugger⁷, Pierre-Yves Dietrich⁸, Regina Mendrzyk¹, Norbert Hilf¹, Oliver Schoor¹, Jens Fritsche¹, Andrea Mahr¹, Dominik Maurer¹, Verona Vass¹, Claudia Trautwein¹, Peter Lewandrowski¹, Christian Flohr¹, Heike Pohla^{9,10}, Janusz J Stanczak¹¹, Vincenzo Bronte¹², Susanna Mandruzzato^{13,14}, Tilo Biedermann¹⁵, Graham Pawelec¹⁶, Evelyn Derhovanessian¹⁶, Hisakazu Yamagishi¹⁷, Tsuneharu Miki¹⁸, Fumiya Hongo¹⁸, Natsuki Takaha¹⁸, Kosei Hirakawa¹⁹, Hiroaki Tanaka¹⁹, Stefan Stevanovic²⁰, Jürgen Frisch¹, Andrea Mayer-Mokler¹, Alexandra Kirner¹, Hans-Georg Rammensee²⁰, Carsten Reinhardt^{1,21} & Harpreet Singh-Jasuja^{1,21}

Vaccination With Patient-Specific Tumor-Derived Antigen in First Remission Improves Disease-Free Survival in Follicular Lymphoma

Stephen J. Schuster, Sattva S. Neelapu, Barry L. Gause, John E. Janik, Franco M. Muggia, Jon P. Gockerman, Jane N. Winter, Christopher R. Flowers, Daniel A. Nikcevich, Eduardo M. Sotomayor, Dean S. McGaughey, Elaine S. Jaffe, Elise A. Chong, Craig W. Reynolds, Donald A. Berry, Carlos F. Santos, Mihaela A. Popa, Amy M. McCord, and Larry W. Kwak



Antigen: Lymphoma Idiotypic (antibody)
conjugates to KLH
Adjuvant: GM-CSF

VOLUME 29 · NUMBER 20 · JULY 10 2011

JOURNAL OF CLINICAL ONCOLOGY

Question

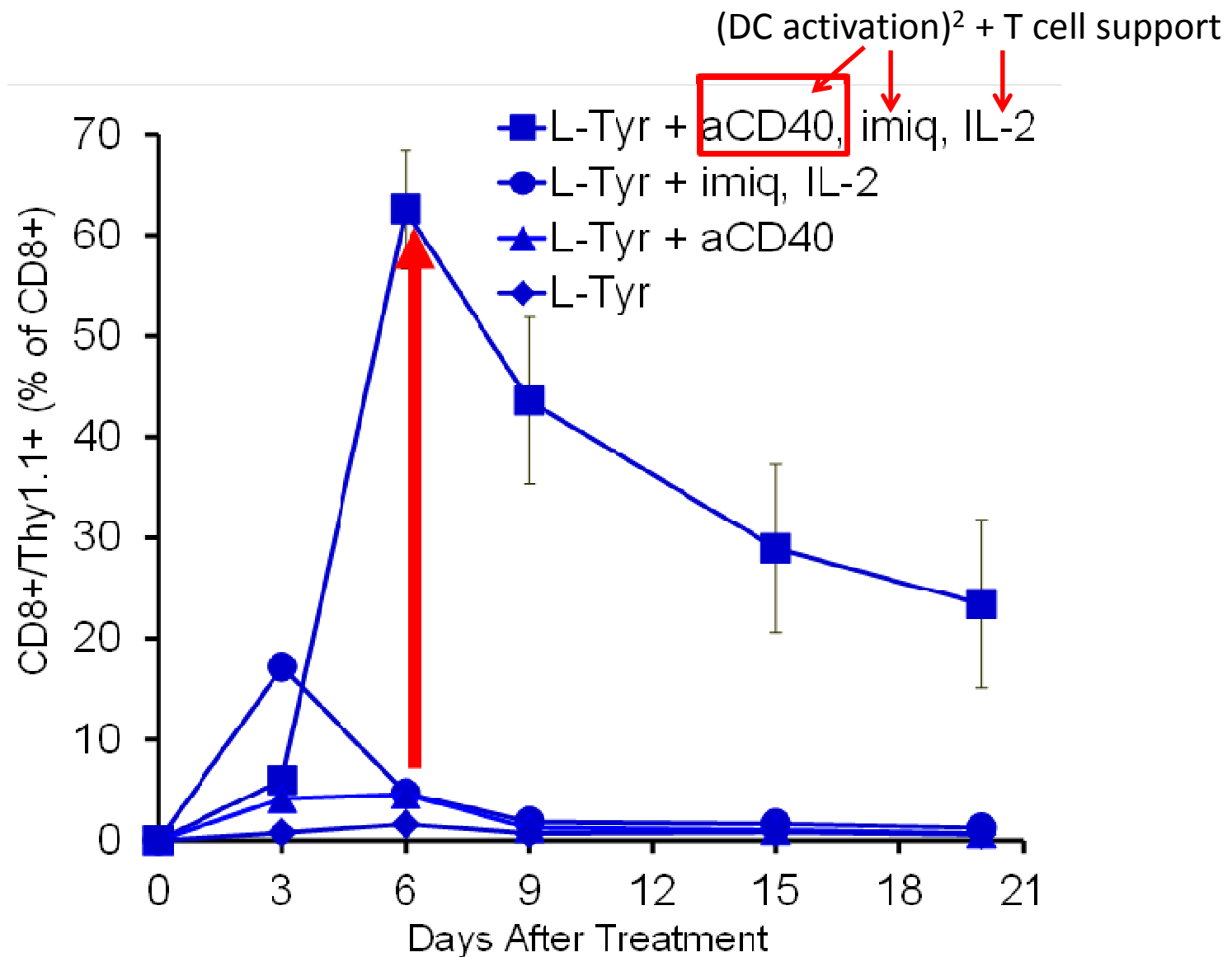
Why do many vaccinated cancer patients not experience tumor regression despite increased levels of cancer-specific T cells?

Question

Why do many vaccinated cancer patients not experience tumor regression despite increased levels of cancer-specific T cells?

- immunosuppressive tumor microenvironment
- too few T cells induced
- poor T cell effector function/wrong phenotype
- poor T cell trafficking to tumor

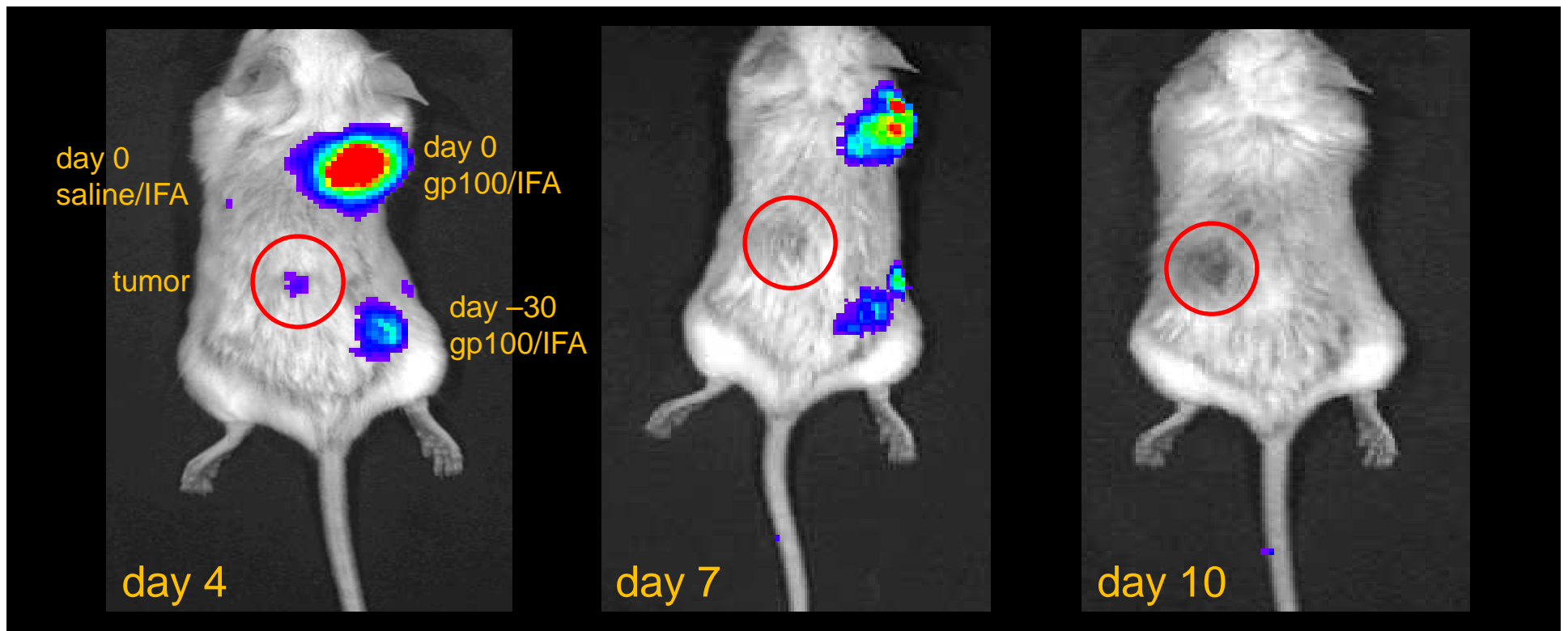
Combination Adjuvants are Key



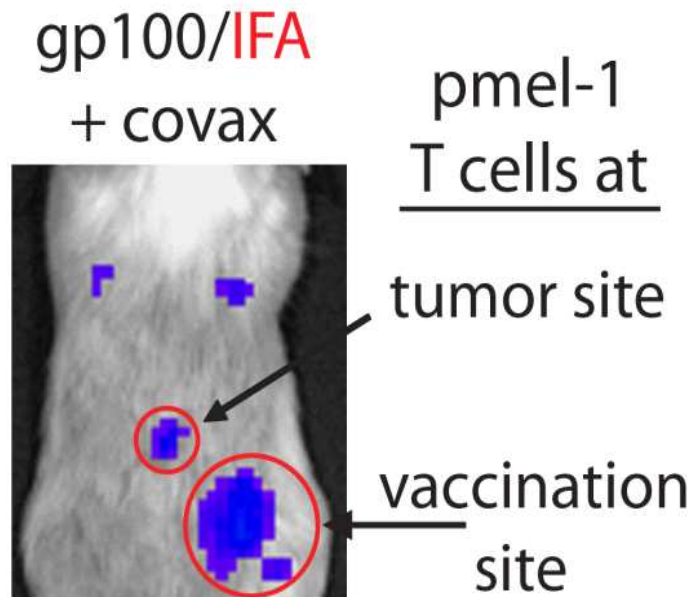
Where are the T cells?

gp100/IFA s.c. + *eLuc*-transduced pmel-1 T cells i.v.

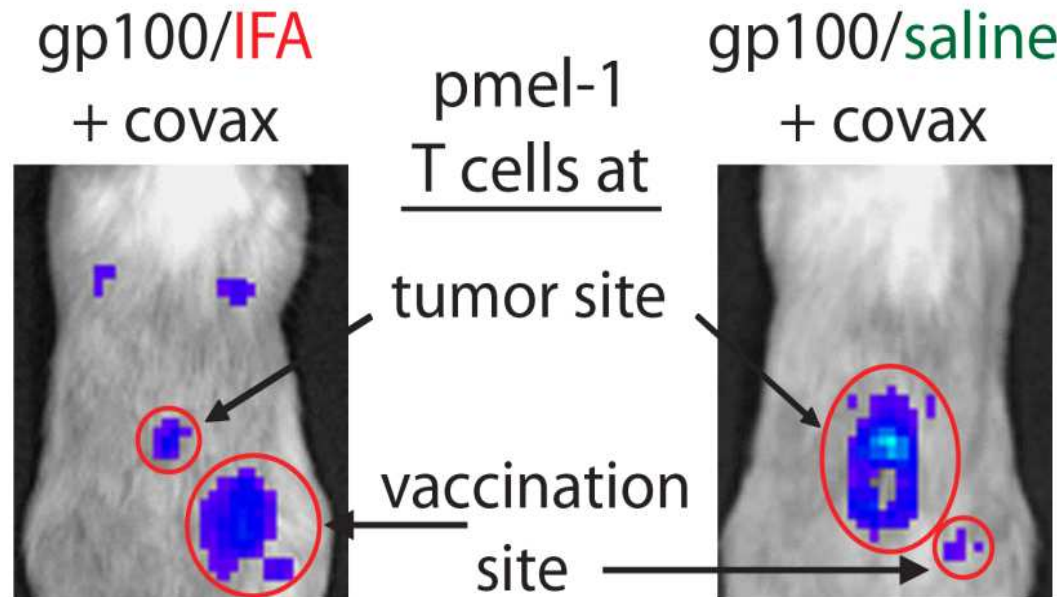
Rabinovich *et al.*, PNAS 2008



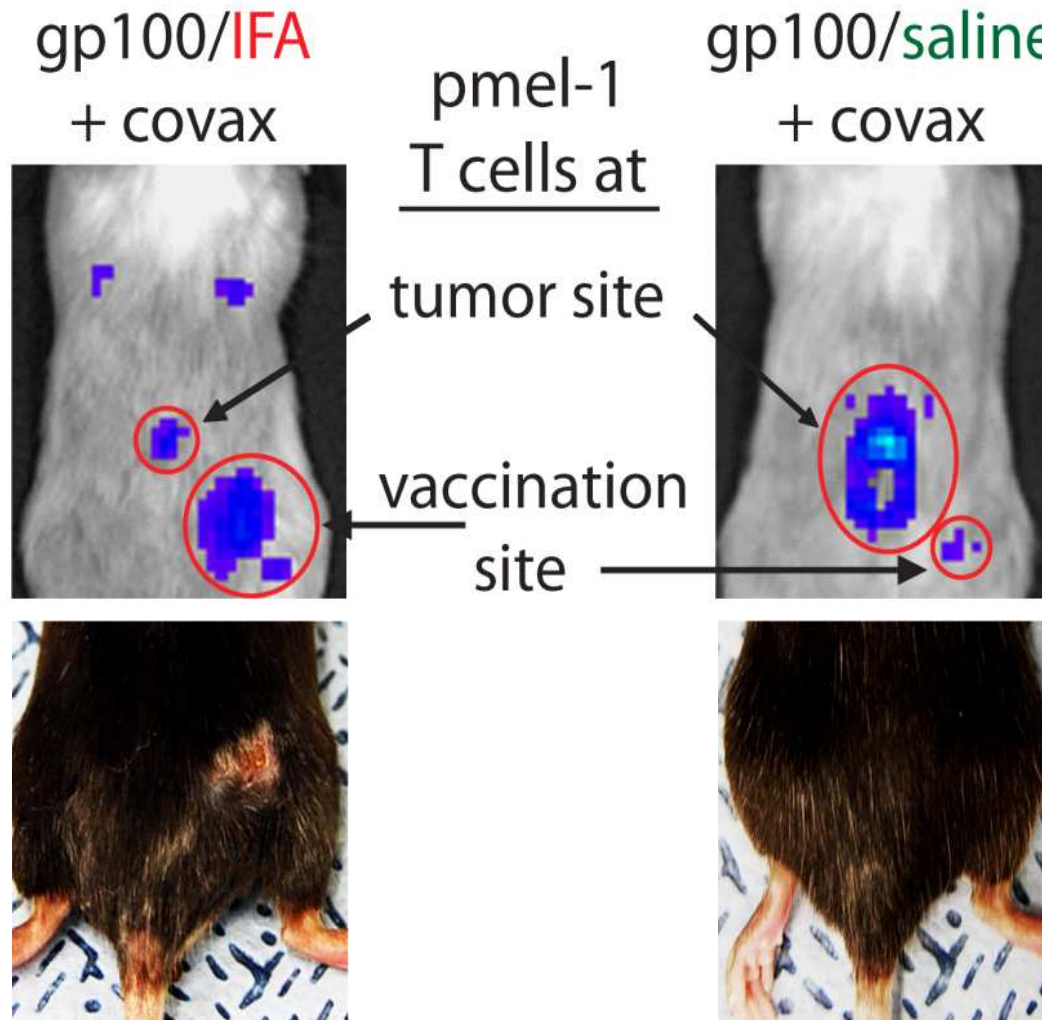
Oil-based vaccines sequester T cells at the vaccination site



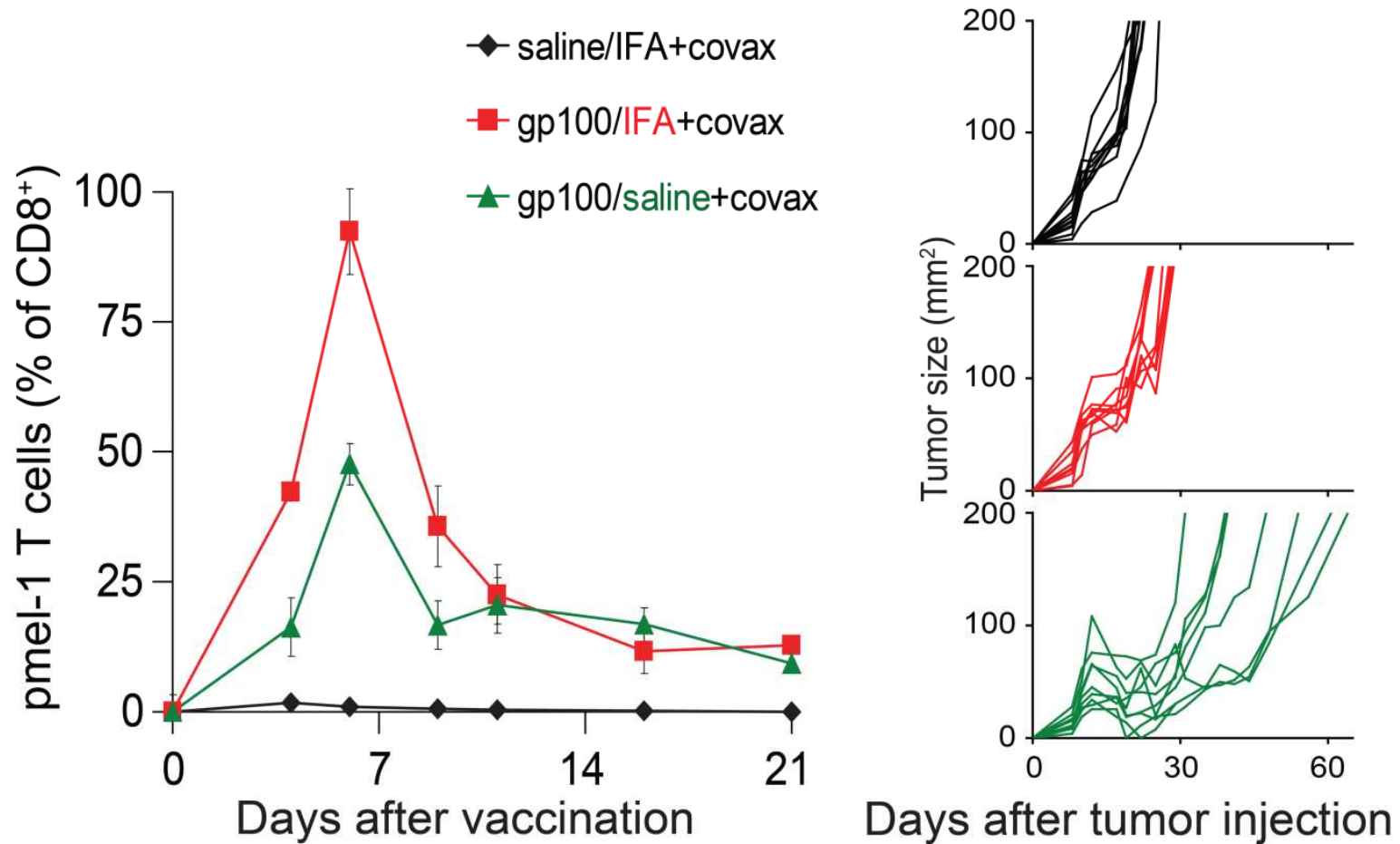
Water-based vaccines permit T cell accumulation in tumor



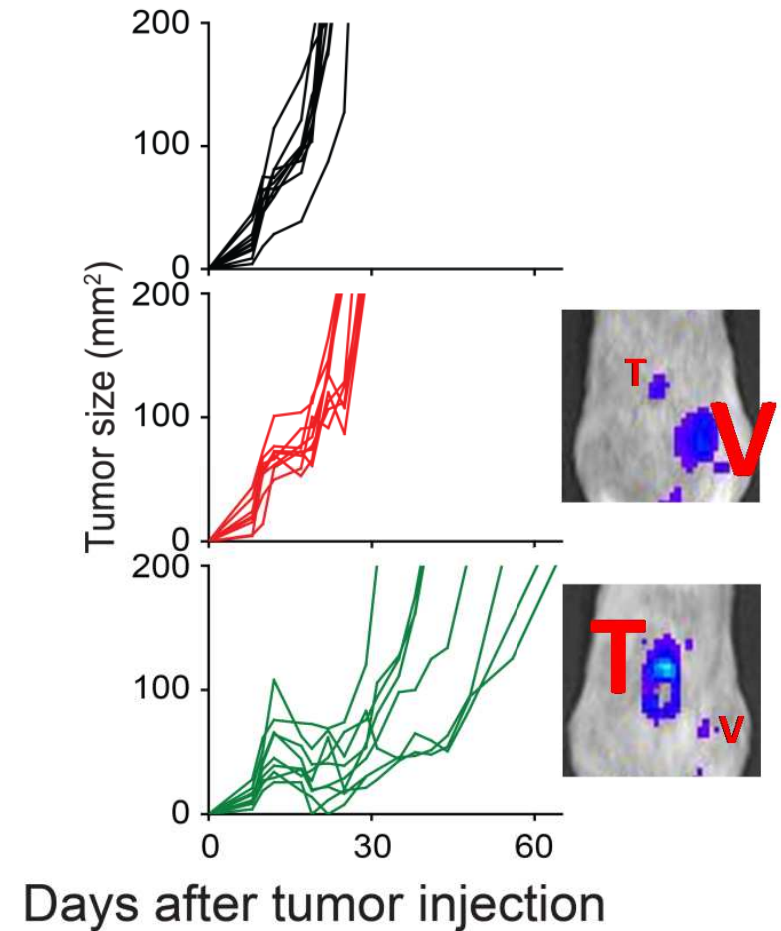
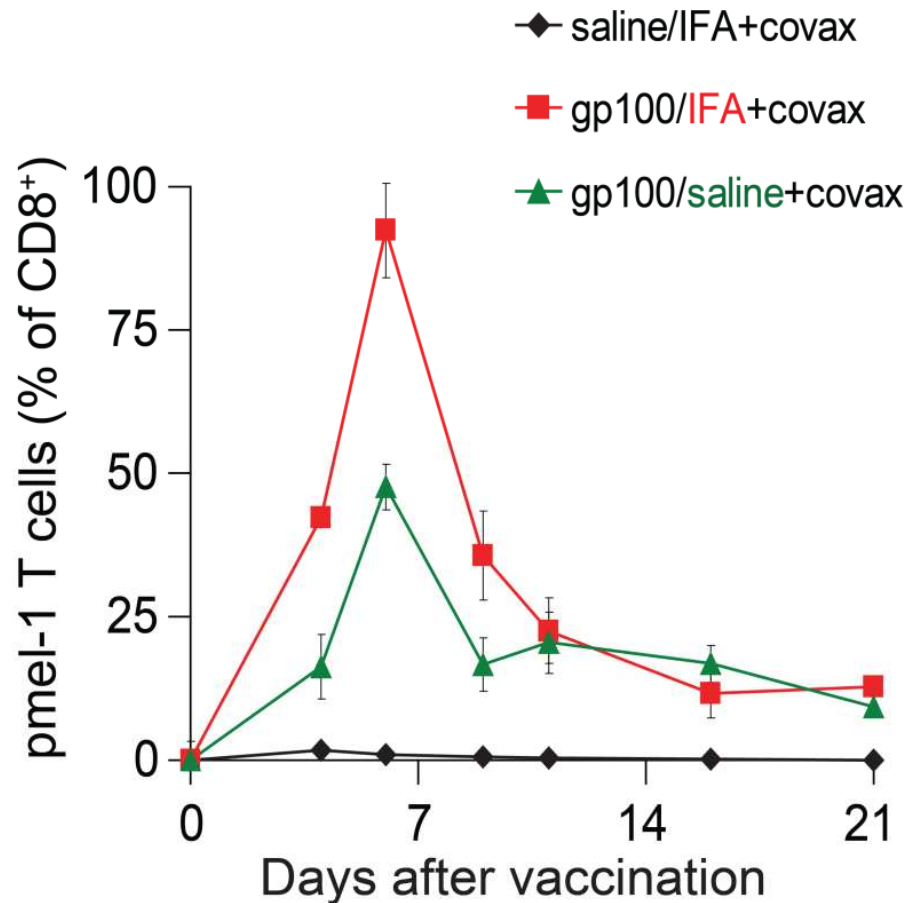
Water-based vaccines permit T cell accumulation in tumor



Tumor therapy with long-lived vs. short-lived vaccine



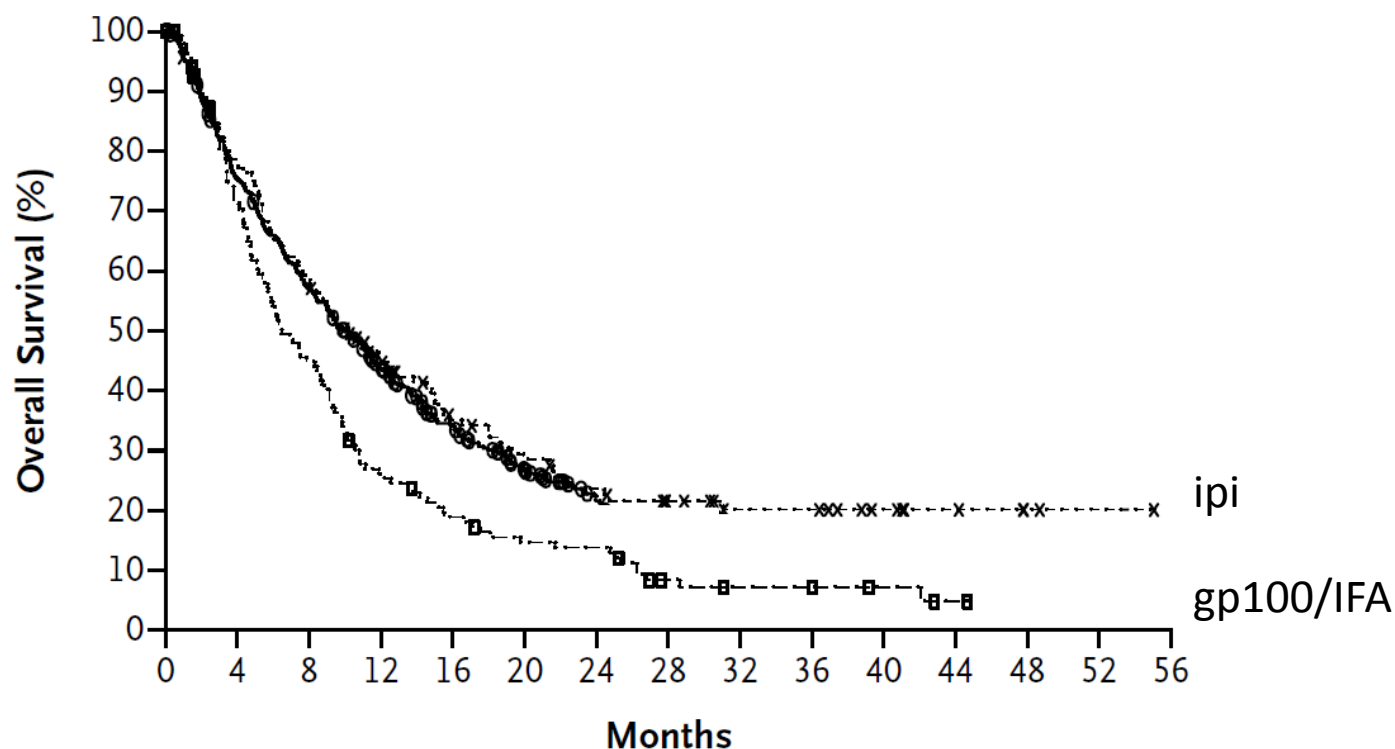
Tumor therapy with long-lived vs. short-lived vaccine



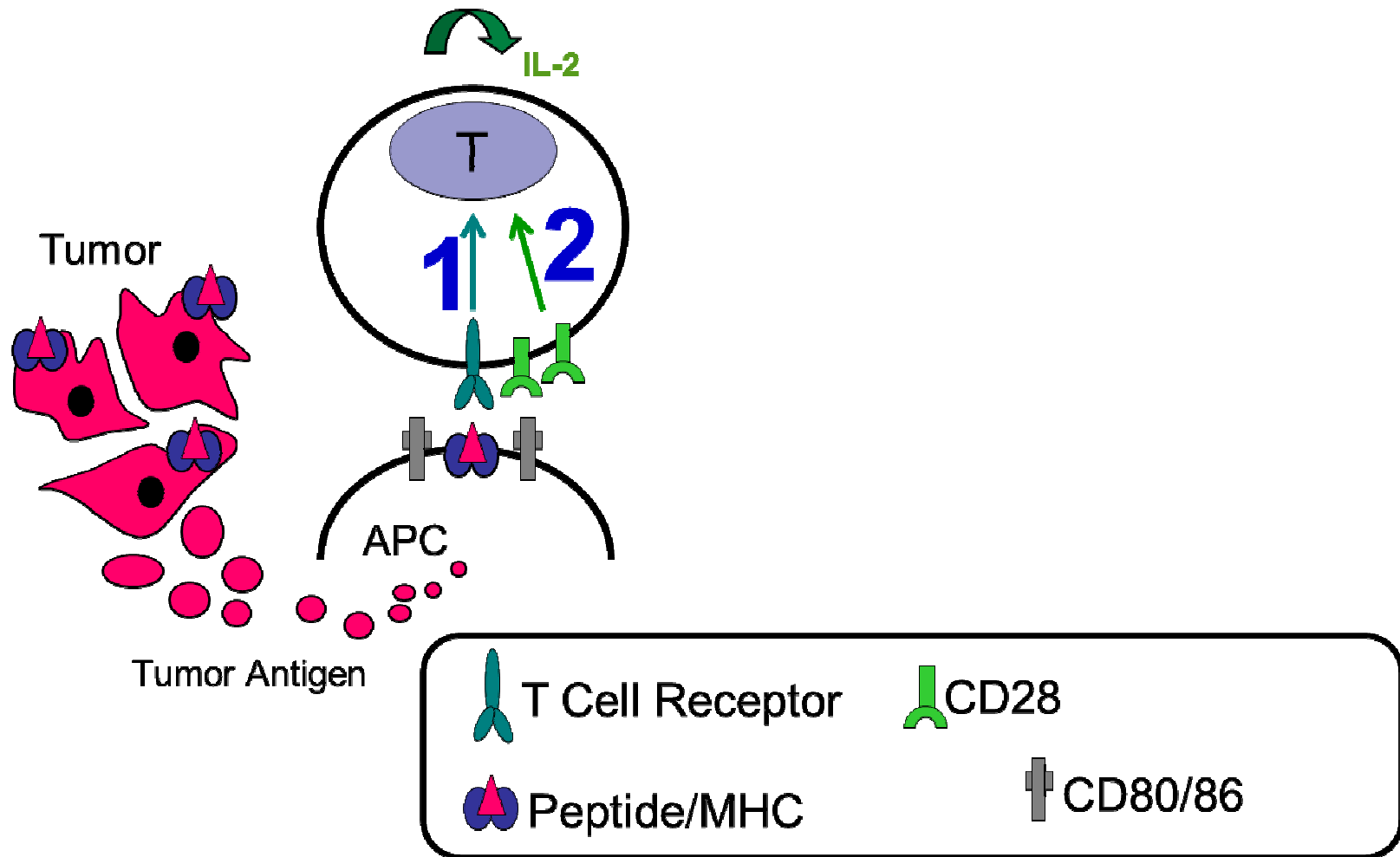
Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akerley, M.D., Alfons J.M. van den Eertwegh, M.D., Ph.D., Jose Lutzky, M.D., Paul Lorigan, M.D., Julia M. Vaubel, M.D., Gerald P. Linette, M.D., Ph.D., David Hogg, M.D., Christian H. Ottensmeier, M.D., Ph.D., Celeste Lebbé, M.D., Christian Peschel, M.D., Ian QUILT, M.D., Joseph I. Clark, M.D., Jedd D. Wolchok, M.D., Ph.D., Jeffrey S. Weber, M.D., Ph.D., Jason Tian, Ph.D., Michael J. Yellin, M.D., Geoffrey M. Nichol, M.B., Ch.B., Axel Hoos, M.D., Ph.D., and Walter J. Urba, M.D., Ph.D.

Overall Survival

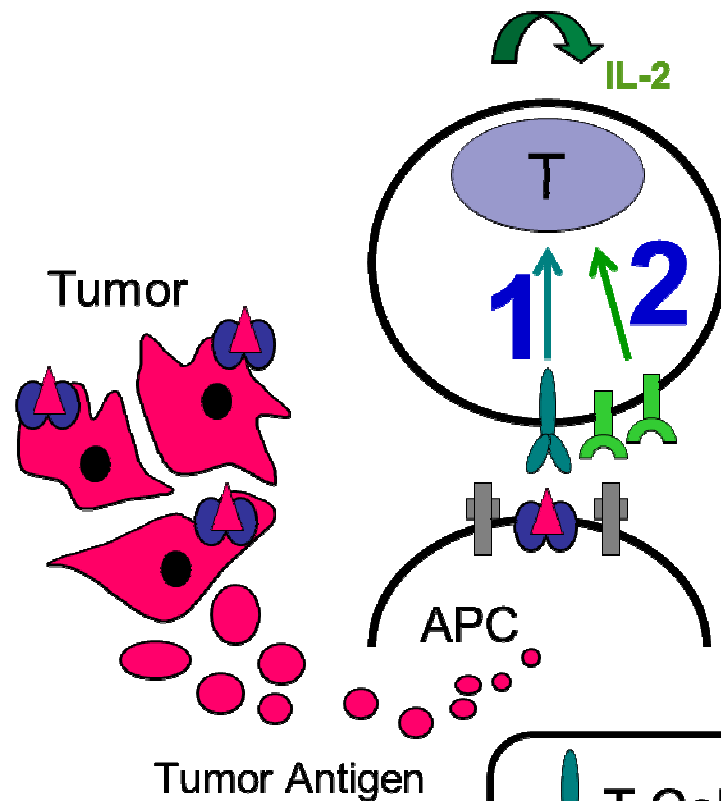


T cell Activation: **2** signals



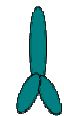
adapted from JP Allison

T cell Activation: **2** signals



Signal **1**: Antigen Recognition

Signal **2**: Costimulation



T Cell Receptor



CD28

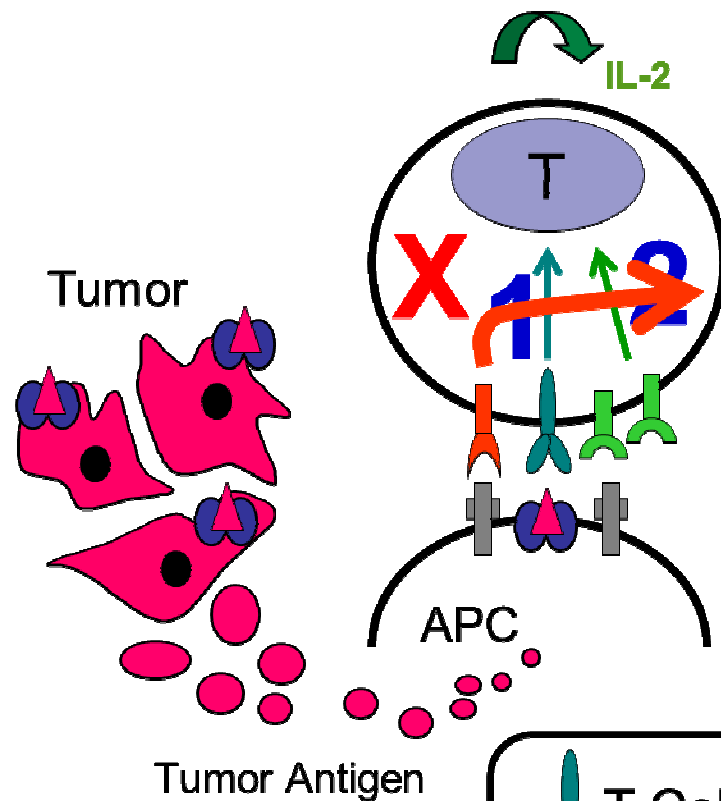


Peptide/MHC



CD80/86

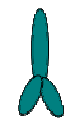
T cell Activation: **2** signals



Signal **1**: Antigen Recognition

Signal **2**: Costimulation

Signal **X**: Checkpoint



T Cell Receptor



CD28



CTLA-4

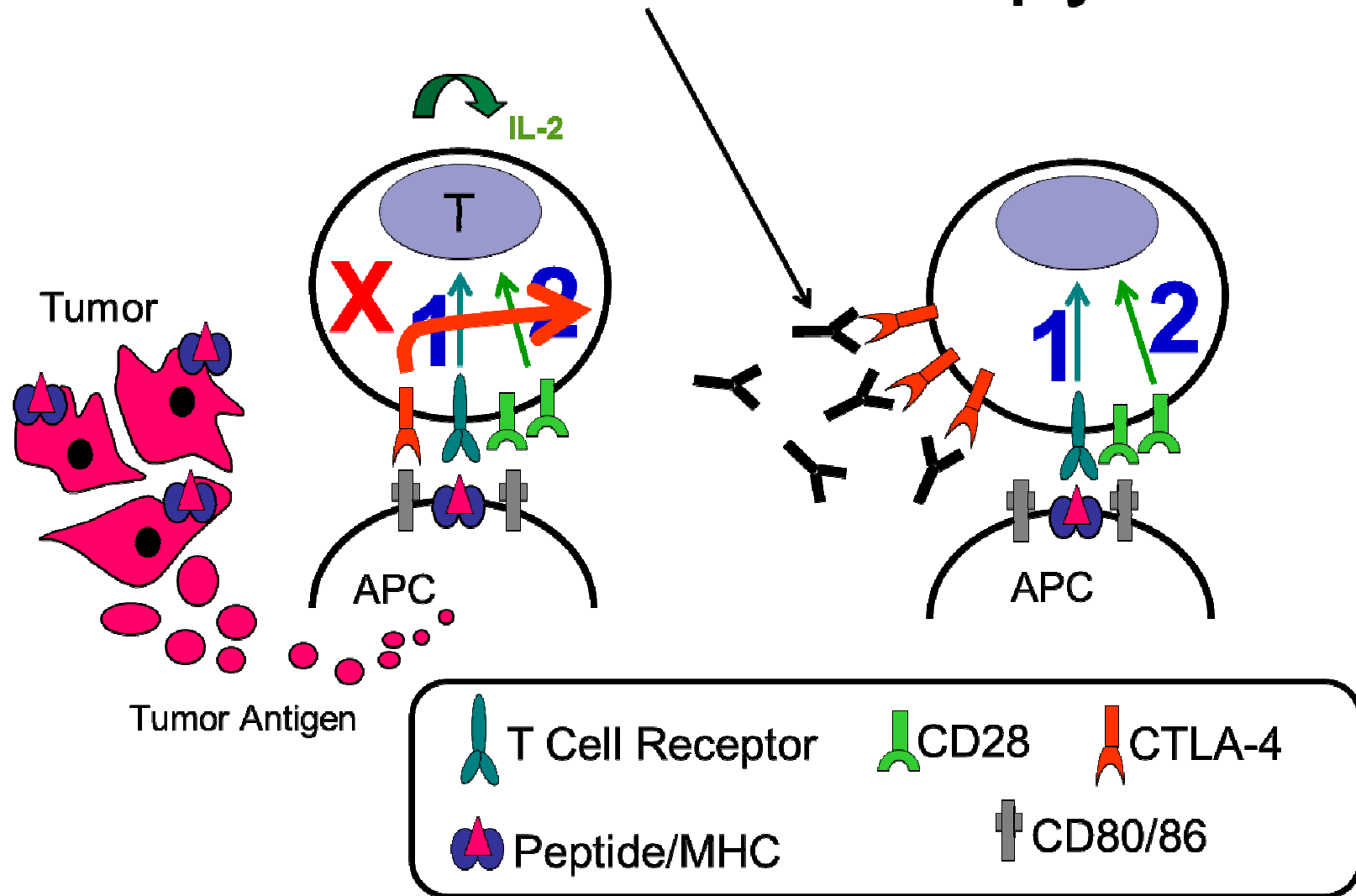


Peptide/MHC



CD80/86

Anti-CTLA-4 therapy



adapted from JP Allison

Checkpoint Blockade + Vaccines

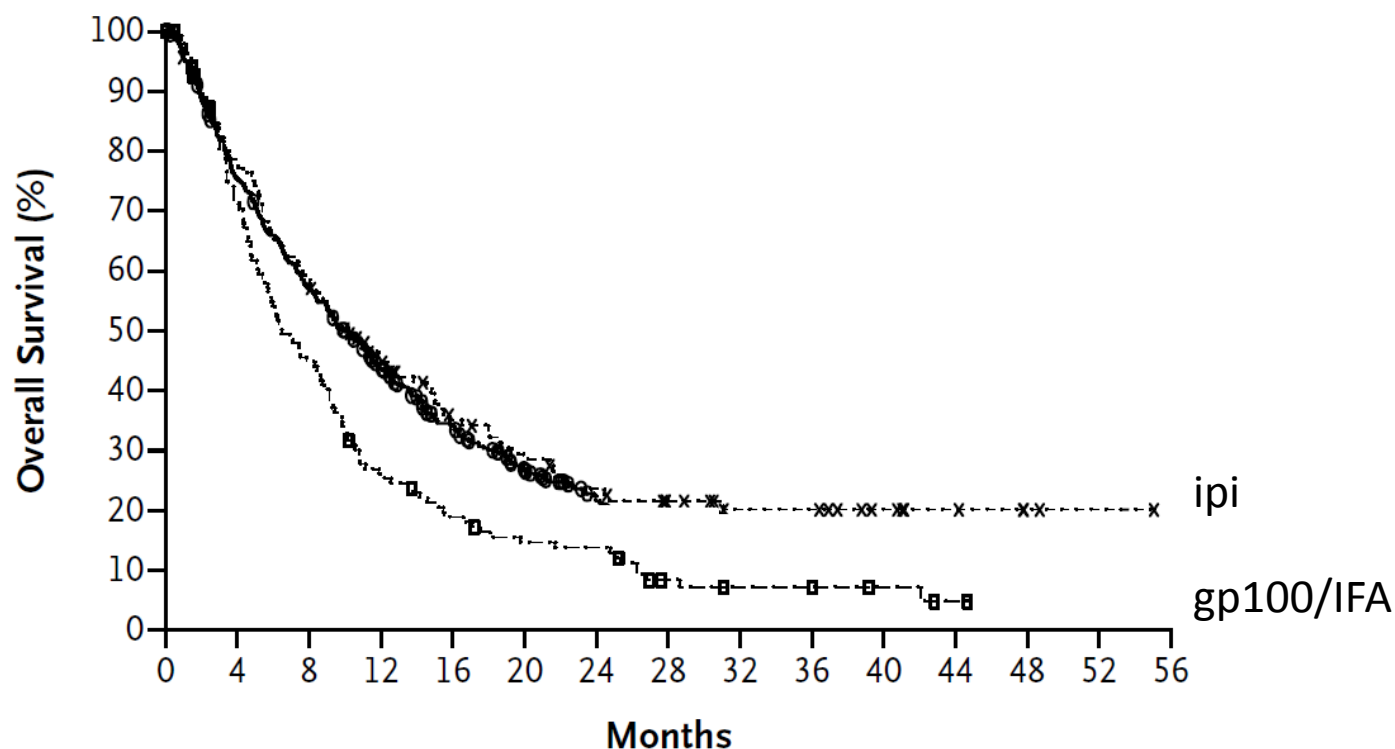
Vaccination and anti-CTLA-4/PD-1 both activate T cells, through different pathways, and could synergize.

However, this was not observed.

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akerley, M.D., Alfons J.M. van den Eertwegh, M.D., Ph.D., Jose Lutzky, M.D., Paul Lorigan, M.D., Julia M. Vaubel, M.D., Gerald P. Linette, M.D., Ph.D., David Hogg, M.D., Christian H. Ottensmeier, M.D., Ph.D., Celeste Lebbé, M.D., Christian Peschel, M.D., Ian QUILT, M.D., Joseph I. Clark, M.D., Jedd D. Wolchok, M.D., Ph.D., Jeffrey S. Weber, M.D., Ph.D., Jason Tian, Ph.D., Michael J. Yellin, M.D., Geoffrey M. Nichol, M.B., Ch.B., Axel Hoos, M.D., Ph.D., and Walter J. Urban, M.D., Ph.D.

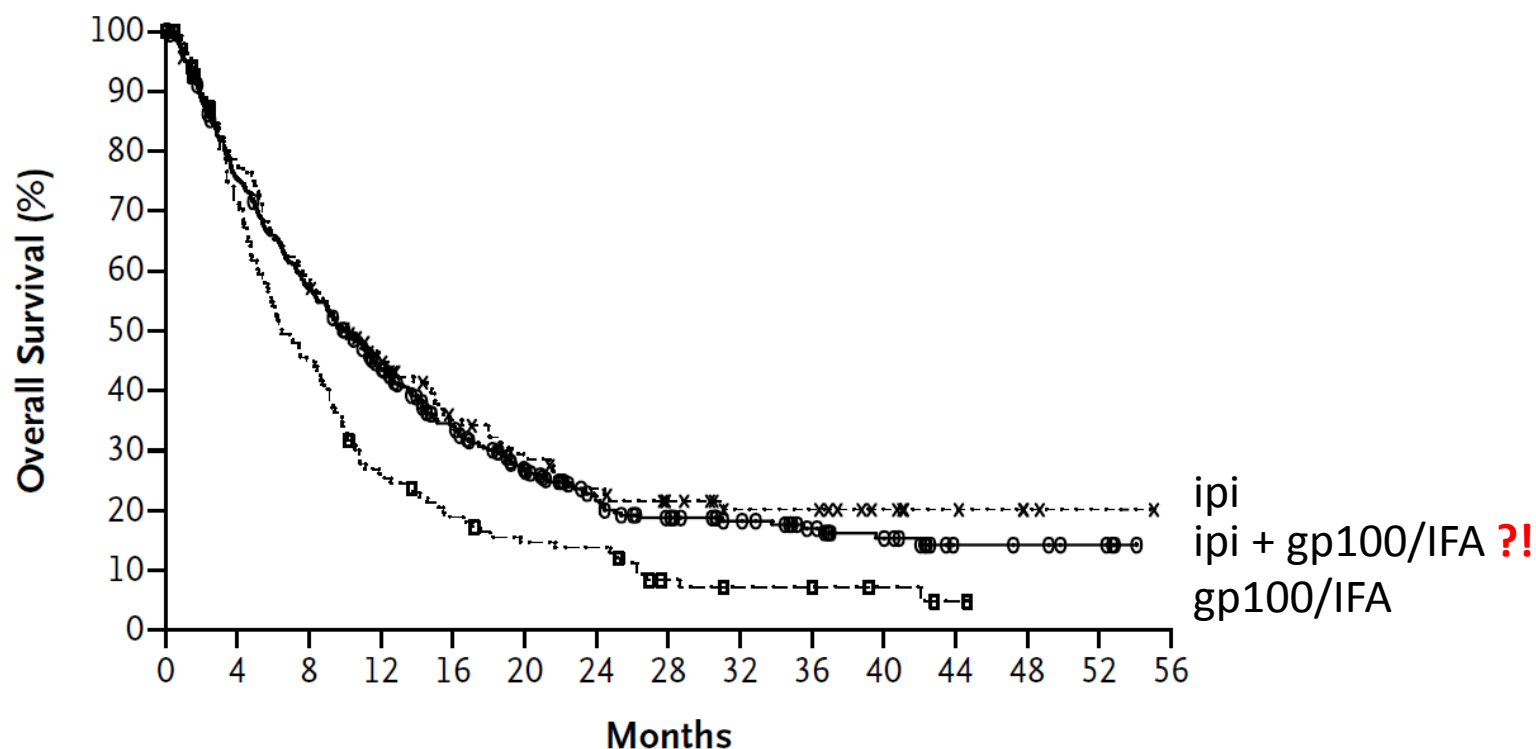
Overall Survival



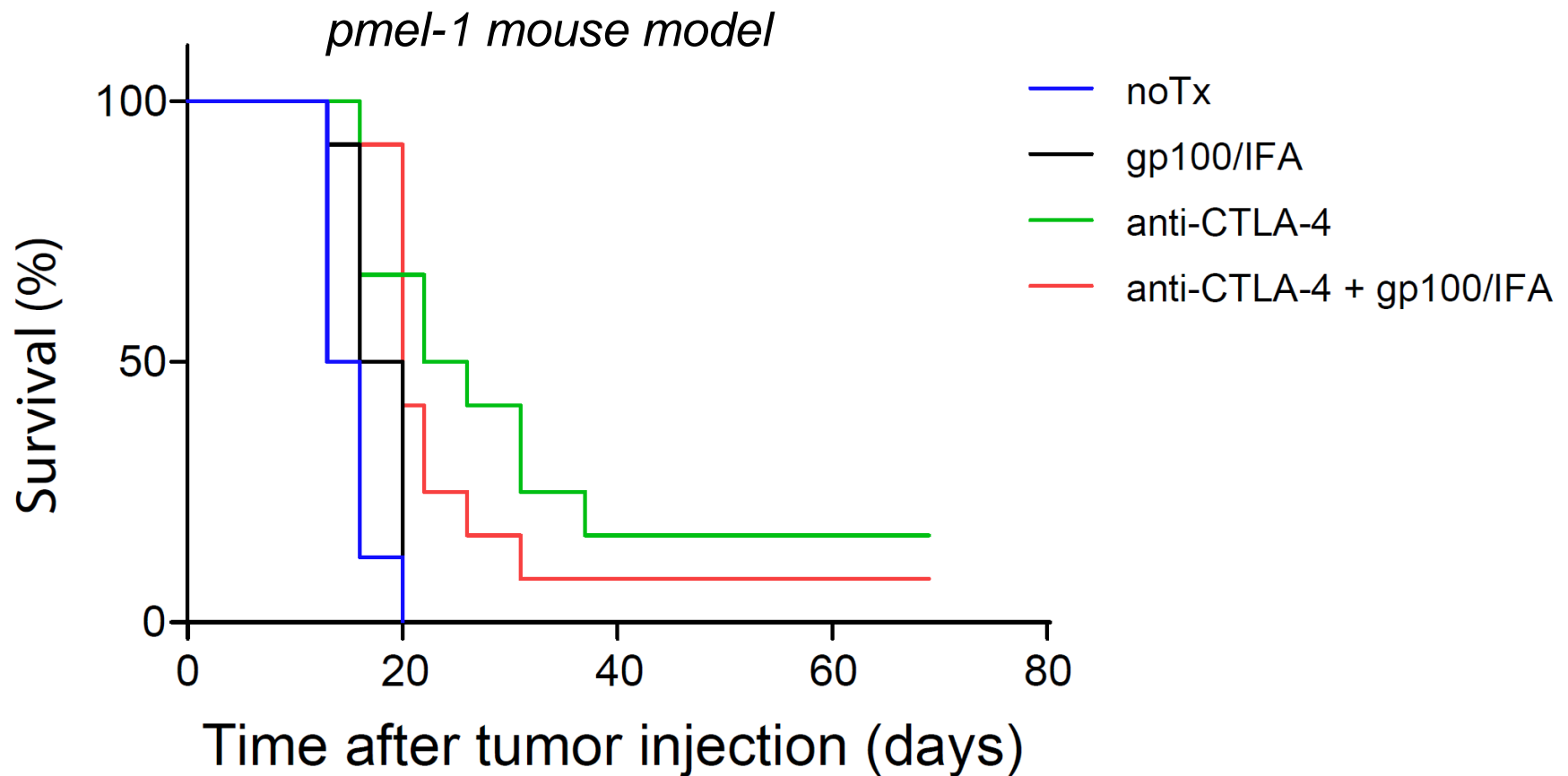
Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akerley, M.D., Alfons J.M. van den Eertwegh, M.D., Ph.D., Jose Lutzky, M.D., Paul Lorigan, M.D., Julia M. Vaubel, M.D., Gerald P. Linette, M.D., Ph.D., David Hogg, M.D., Christian H. Ottensmeier, M.D., Ph.D., Celeste Lebbé, M.D., Christian Peschel, M.D., Ian QUILT, M.D., Joseph I. Clark, M.D., Jedd D. Wolchok, M.D., Ph.D., Jeffrey S. Weber, M.D., Ph.D., Jason Tian, Ph.D., Michael J. Yellin, M.D., Geoffrey M. Nichol, M.B., Ch.B., Axel Hoos, M.D., Ph.D., and Walter J. Urba, M.D., Ph.D.

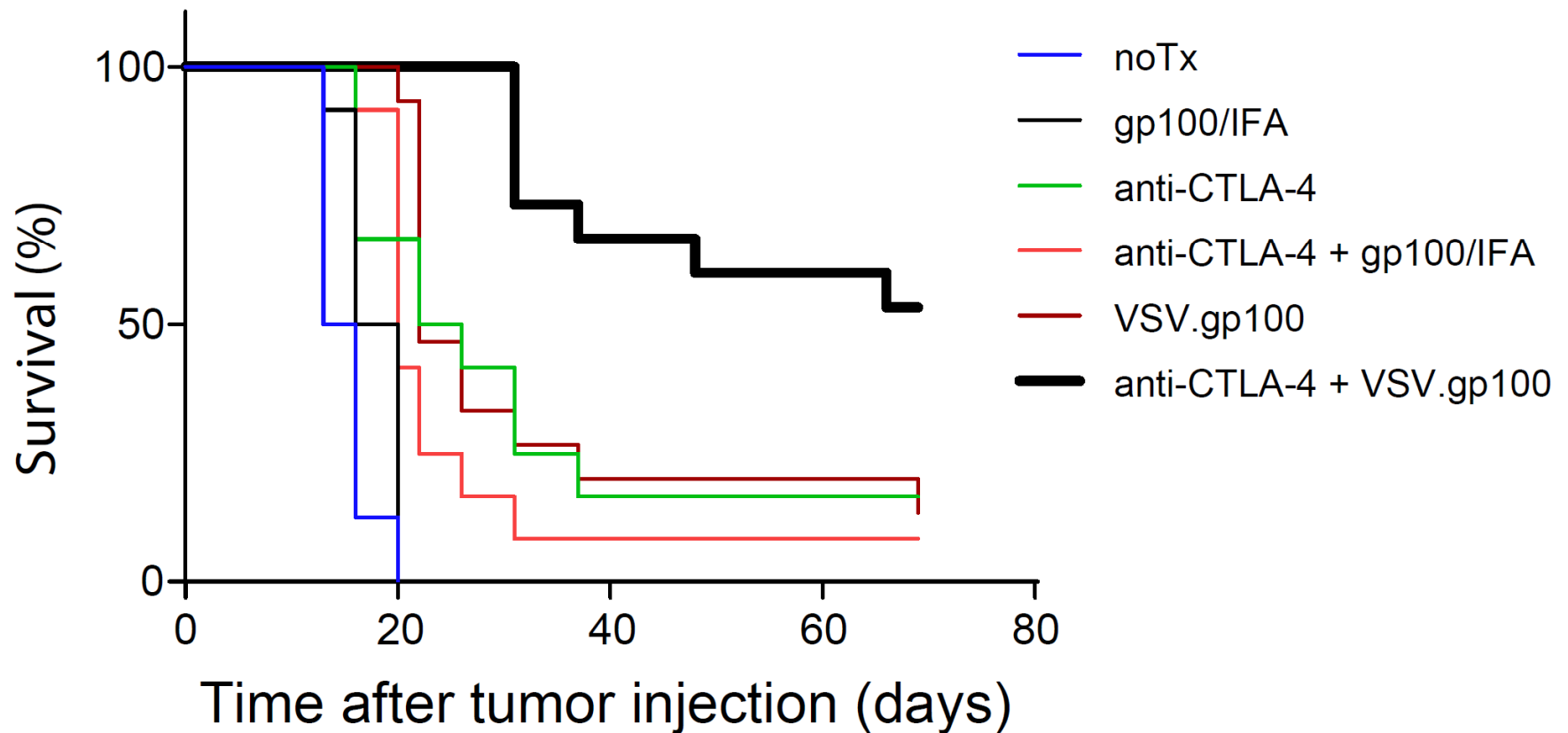
Overall Survival



IFA-based vaccination does not synergize with anti-CTLA-4 therapy



Virus-based vaccination synergizes with anti-CTLA-4 therapy



Conclusions

- Cancer vaccines can have clinical impact
- T cell responses tend to be (too) low or dysfunctional

To induce better T cell / clinical responses:

- Identify potent antigens: mutations/overexpressed
- Formulation matters: possible T cell sequestration
- Add immunomodulators (cytokines, TLR agonists)
- Combination Vaccines: Multiple Immunostimulatory Molecules
- Combine with CTLA-4/PD-1 checkpoint blockade