Cancer Immunotherapy:

Active Immunization Approaches

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MD Anderson Cancer Center
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Disclosures

- No relevant financial relationships to disclose.

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**

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- **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?

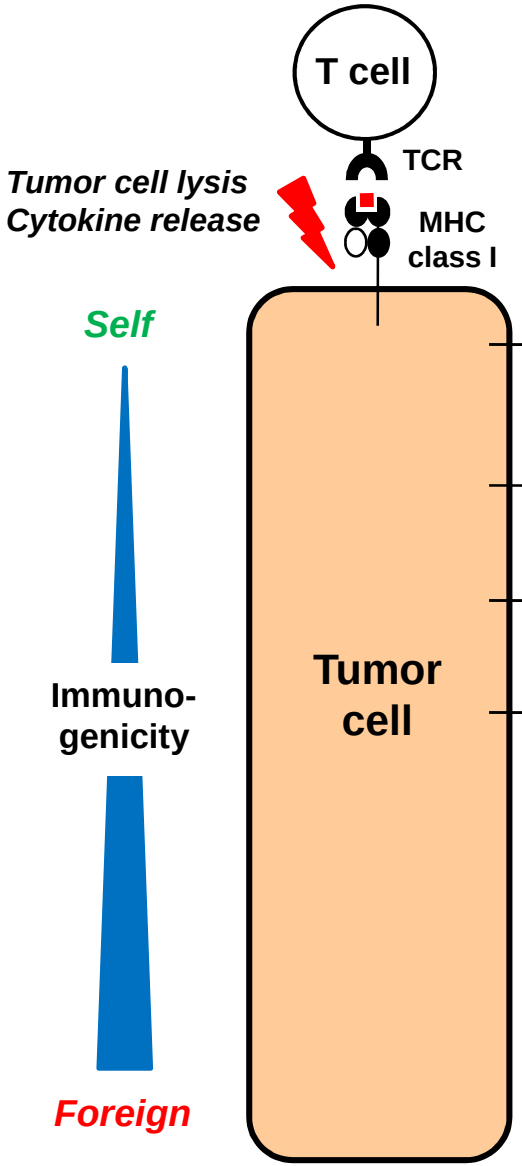
A **preparation** of a **tumor antigen** (usually protein) that upon administration stimulates tumor-specific antibodies and/or T cells

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

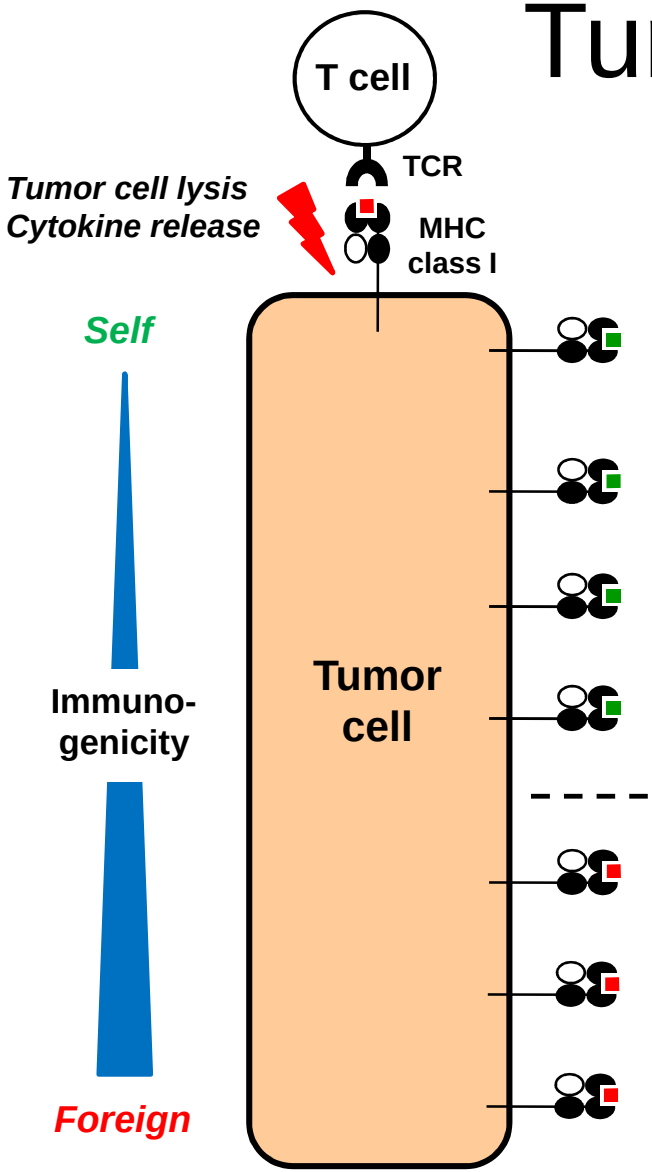


Non-mutated antigens (normal)

- → **Self Ags - ubiquitous, not tumor-specific (eg. actin, vimentin) > *98%***
- → **Tissue differentiation Ags (eg. gp100, Tyrosinase, MART-1/Melan-A)**
- → **Cancer / testis Ags (eg. MAGE, GAGE, NY-ESO-1)**
- → **Over-expressed in tumors (eg. KIT, HER2, HERV)**

Adapted from Dr. Gregory Lizee, Melanoma Med. Oncol.

Tumor-Associated Antigens



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→ **Cancer / testis Ags (eg. MAGE, GAGE, NY-ESO-1)**

→ **Over-expressed in tumors (eg. KIT, HER2, HERV)**

→ **Single point mutations**

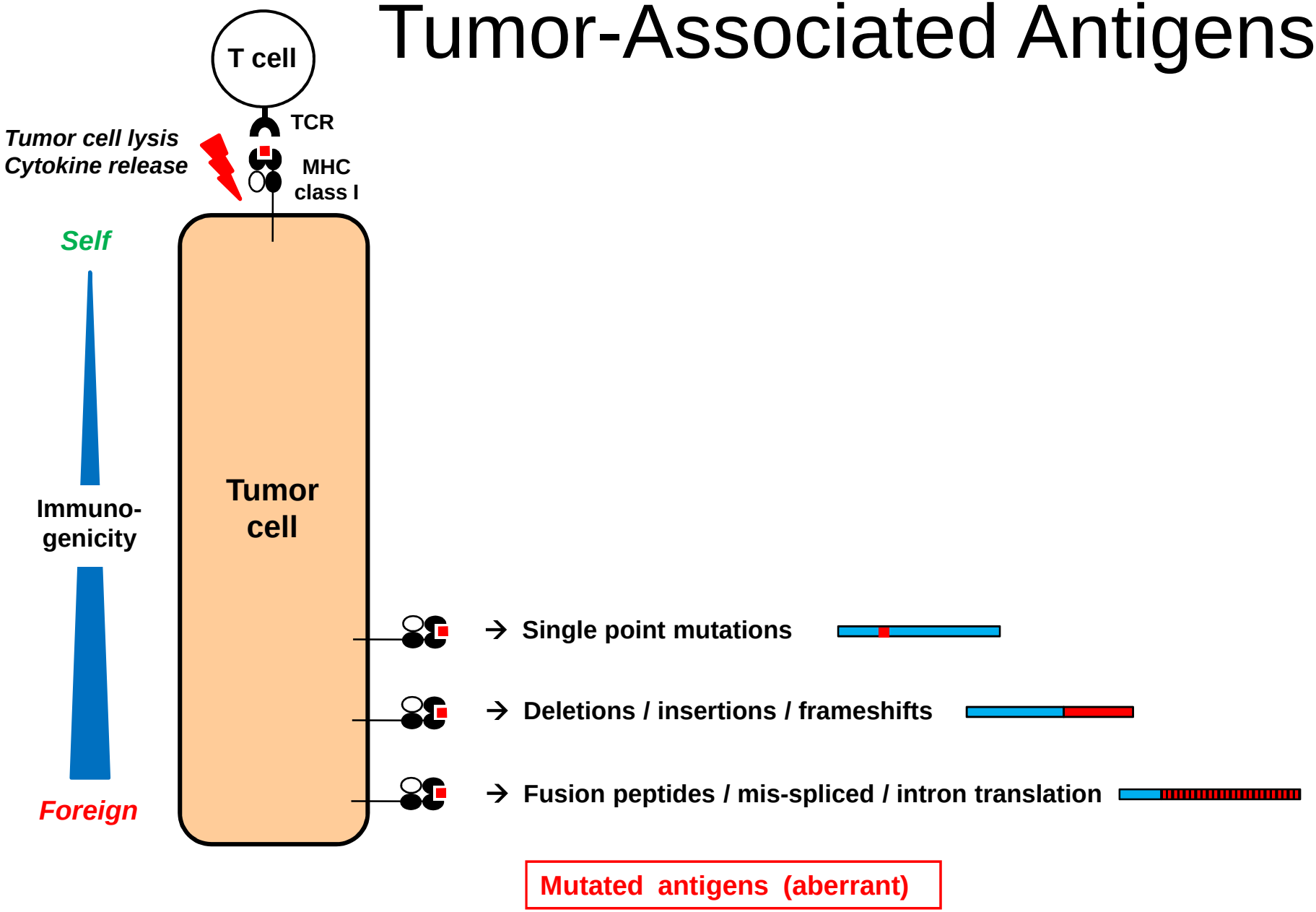
→ **Deletions / insertions / frameshifts**

→ **Fusion peptides / mis-spliced / intron translation**

Mutated antigens (aberrant)

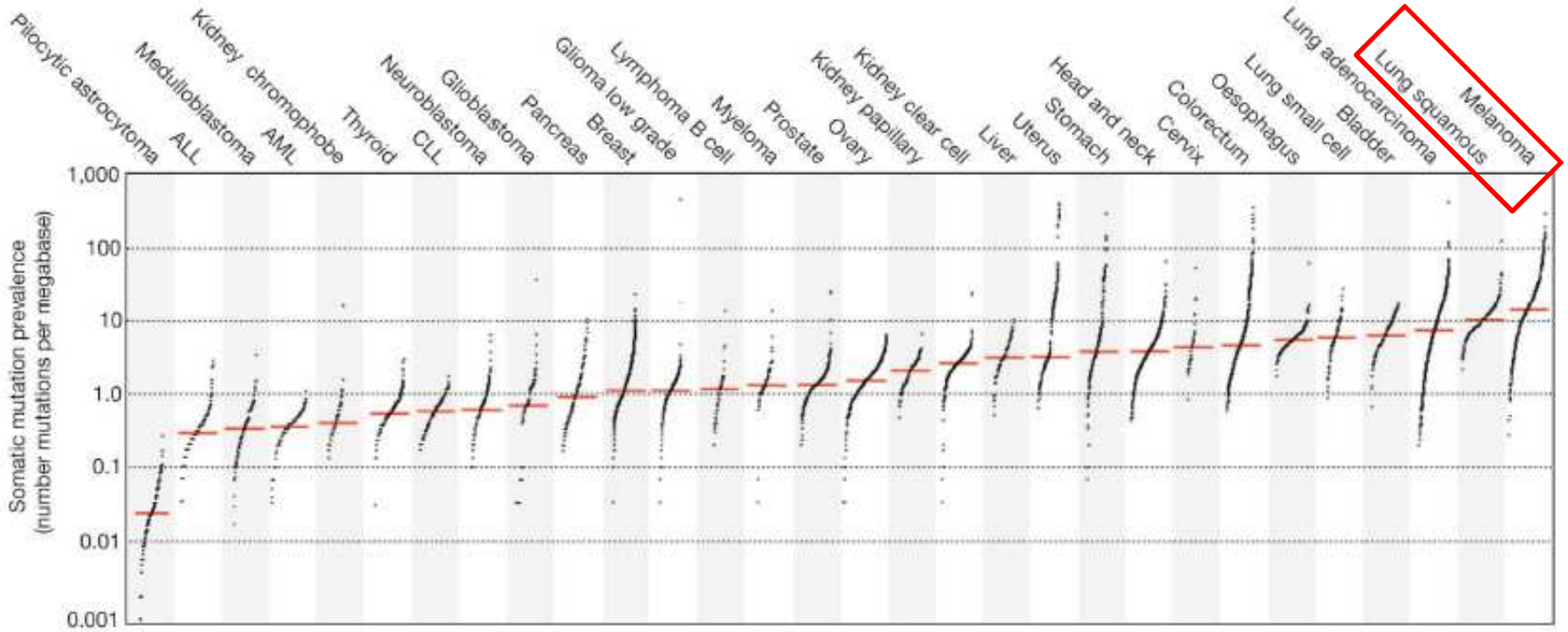
Adapted from Dr. Gregory Lizee, Melanoma Med. Oncol.

Tumor-Associated Antigens



Adapted from Dr. Gregory Lizee, Melanoma Med. Oncol.

The prevalence of somatic mutations across human cancer types



Signatures of mutational processes in human cancer Alexandrov et al.

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

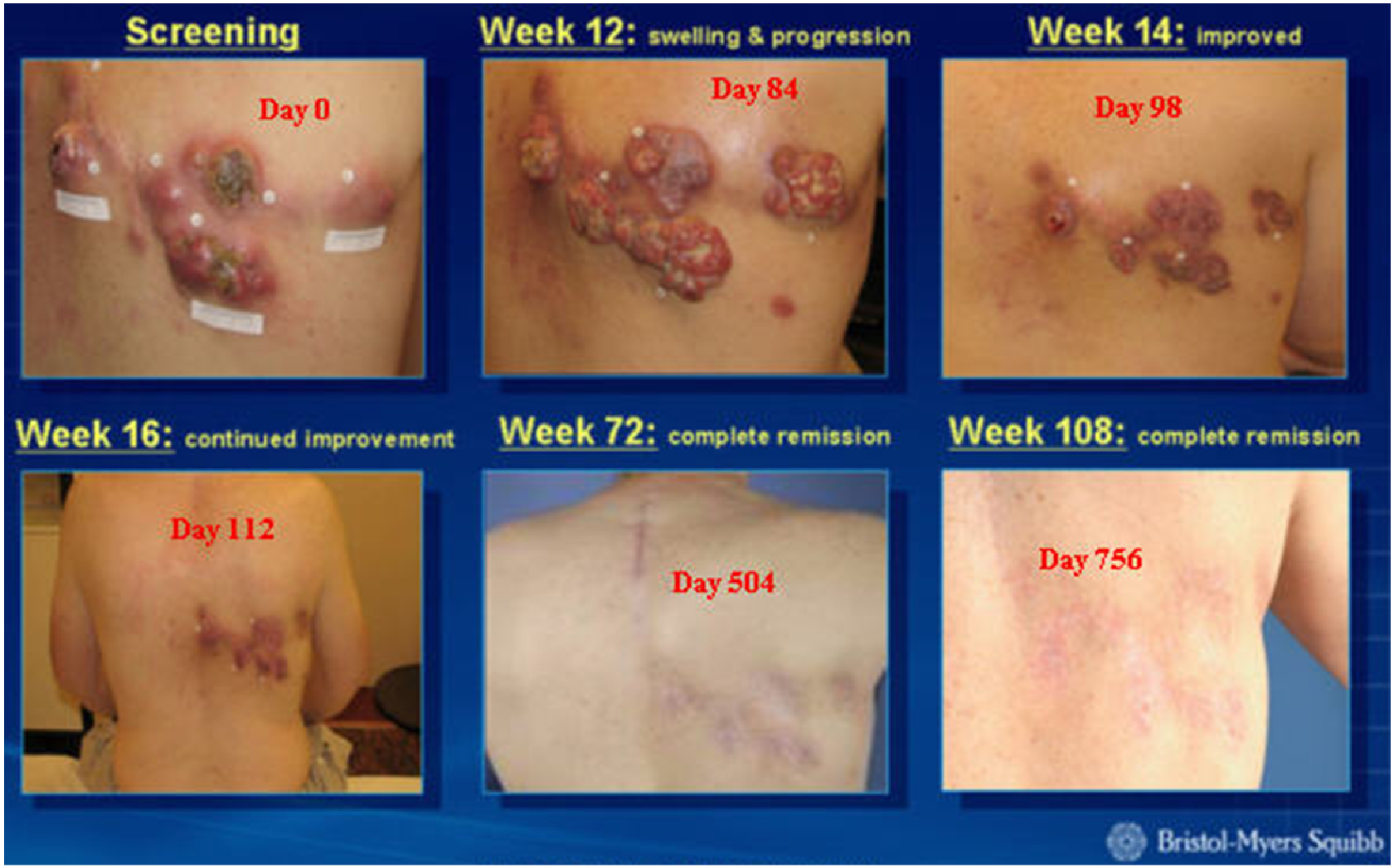
The NEW ENGLAND JOURNAL of MEDICINE

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



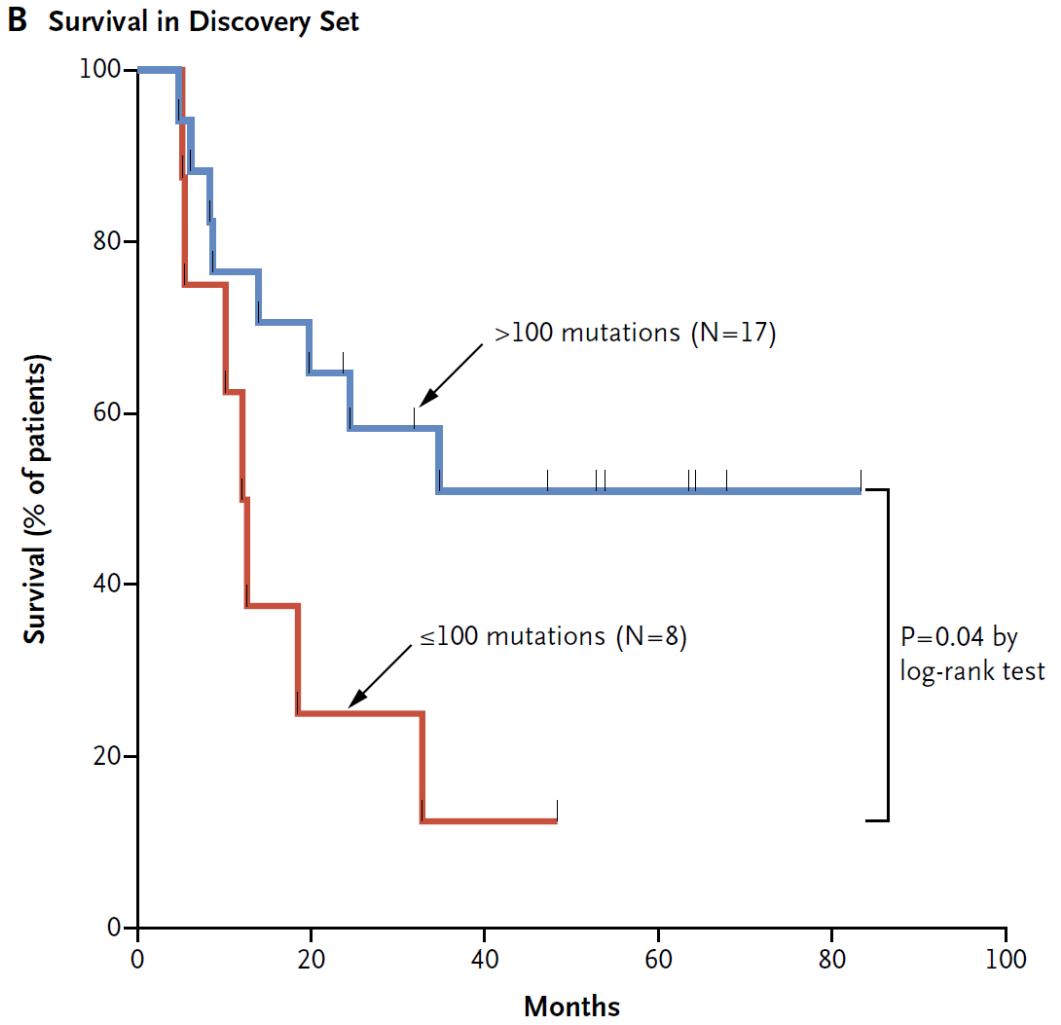
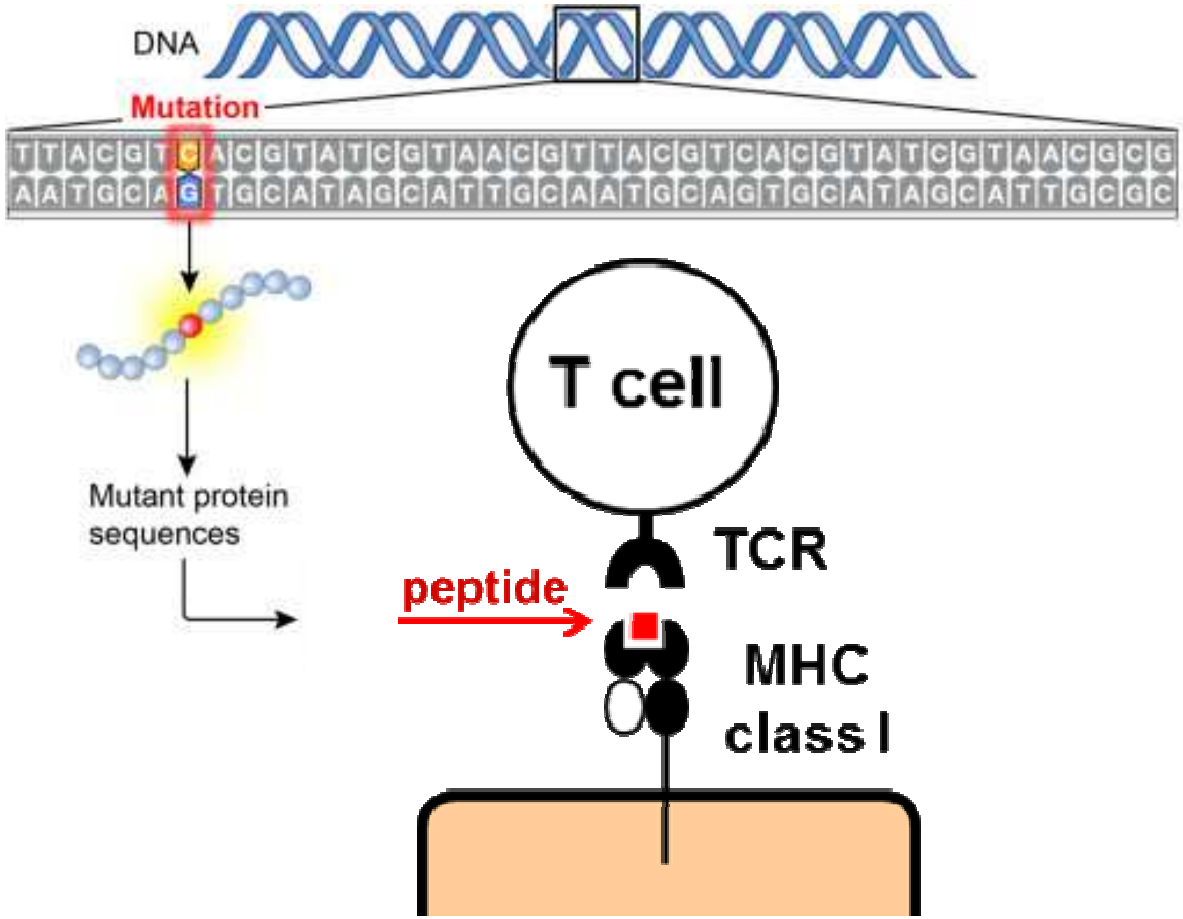
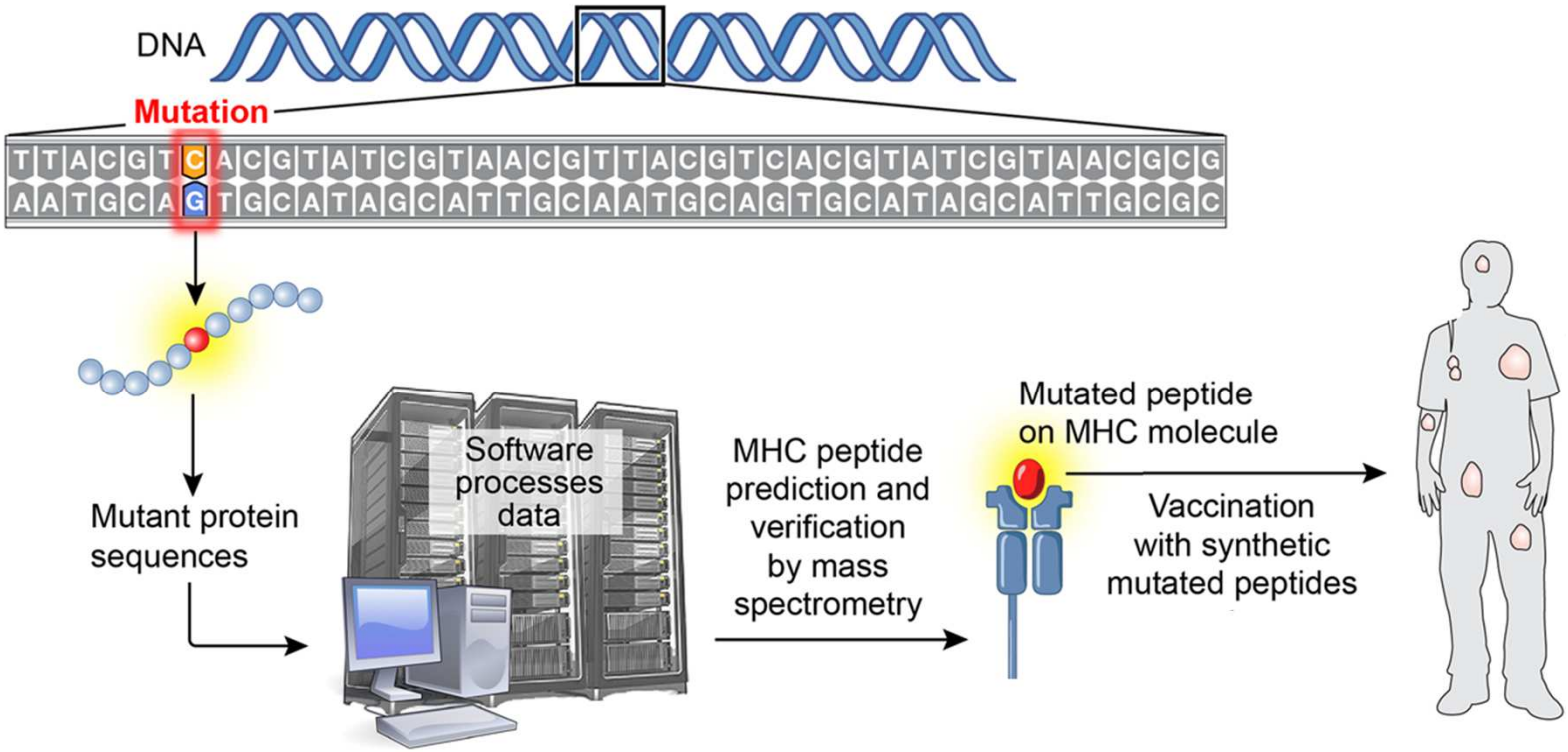


Figure 2. Mutational Landscape of Tumors According to Clinical Benefit from Ipilimumab Treatment.

Mutated Peptides as Cancer Antigens



From Mutation to Vaccine



adapted from Overwijk *et al.*, JITC, 2013

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

The NEW ENGLAND JOURNAL of MEDICINE

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

Schwartzentruber *et al*., NEJM 2011

Peptide-based Cancer Vaccines

The NEW ENGLAND JOURNAL of MEDICINE

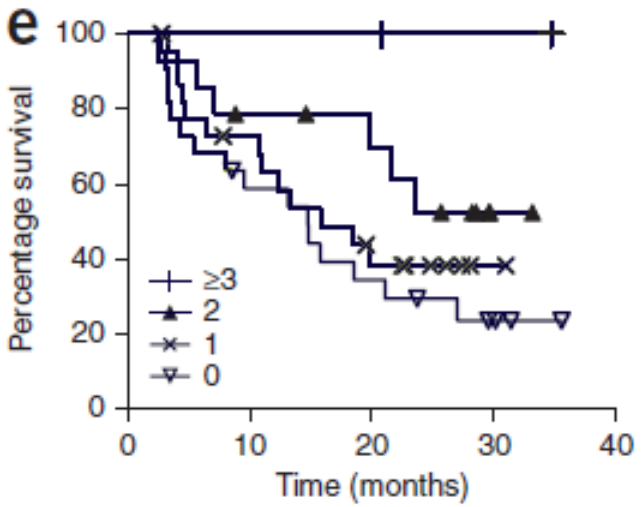
ORIGINAL ARTICLE

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. Fathers, 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



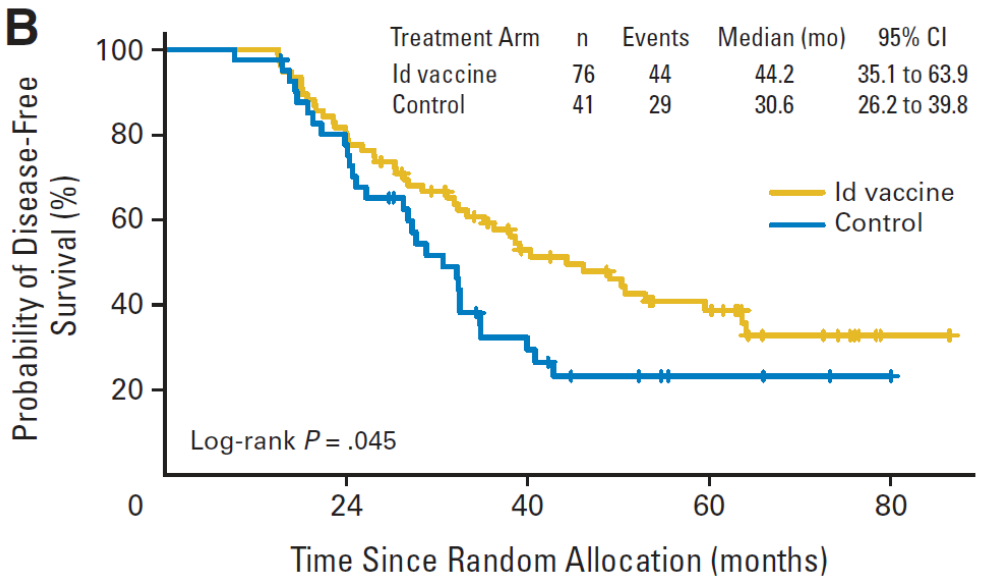
nature medicine AUGUST 2012

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 Stenzl[2], Romuald Zdrojowy[3], Anna Pluzanska[4], Cezary Szczylik[5], Michael Staehler[6], Wolfram Brugger[7], Pierre-Yves Dietrich[8], Regina Mendrzyk[1], Norbert Hilf[1], Oliver Schoor[1], Jens Fritsche[1], Andrea Mahr[1], Dominik Maurer[1], Verona Vass[1], Claudia Trautwein[1], Peter Lewandrowski[1], Christian Flohr[1], Heike Pohla[9,10], Janusz J Stanczak[11], Vincenzo Bronte[12], Susanna Mandruzzato[13,14], Tilo Biedermann[15], Graham Pawelec[16], Evelyna Derhovanessian[16], Hisakazu Yamagishi[17], Tsuneharu Miki[18], Fumiya Hongo[18], Natsuki Takaha[18], Kosei Hirakawa[19], Hiroaki Tanaka[19], Stefan Stevanovic[20], Jürgen Frisch[1], Andrea Mayer-Mokler[1], Alexandra Kirner[1], Hans-Georg Rammensee[20], 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 Idiotype (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?

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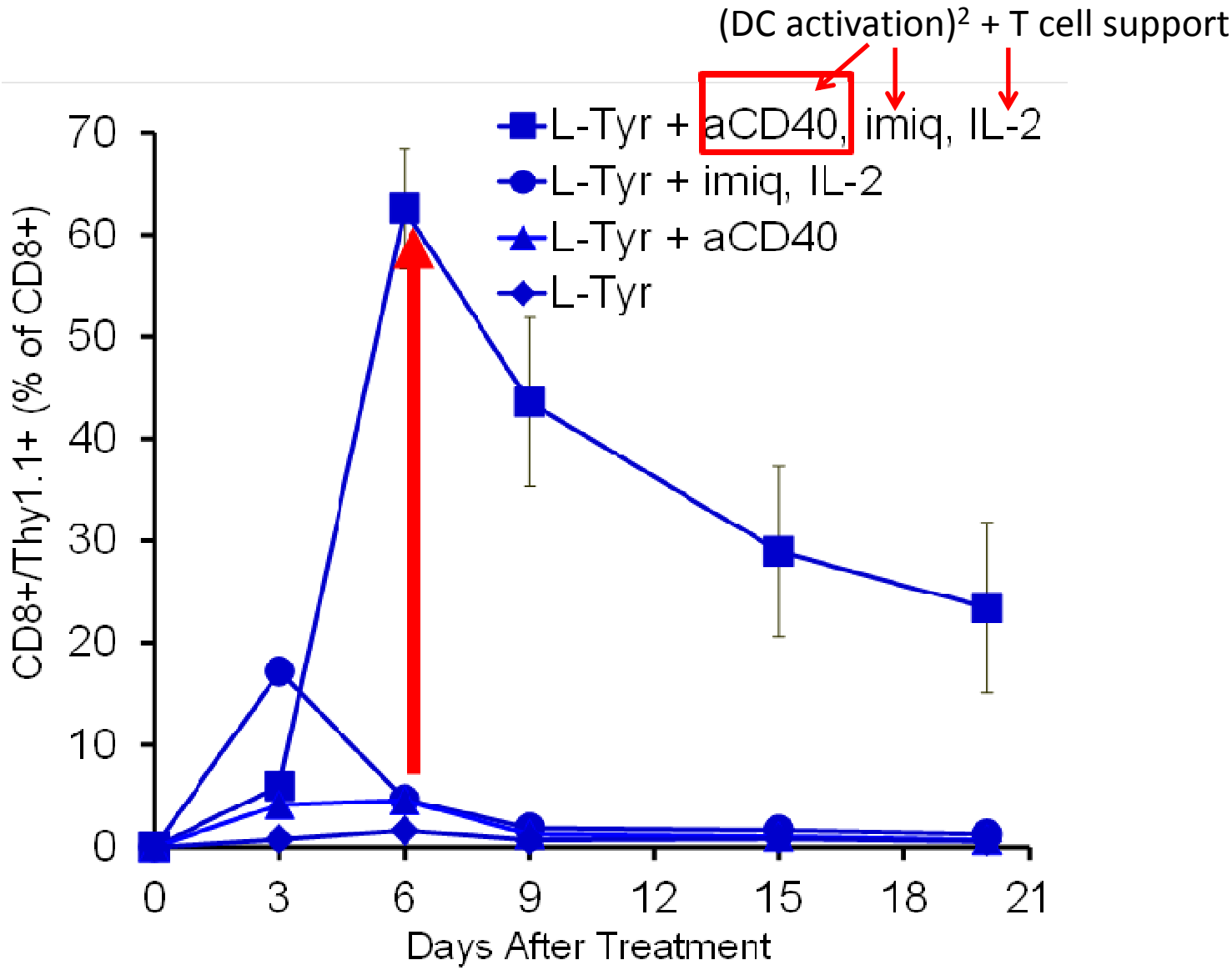
Why do many vaccinated cancer patients not experience tumor regression despite increased levels of cancer-specific T cells?

- 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

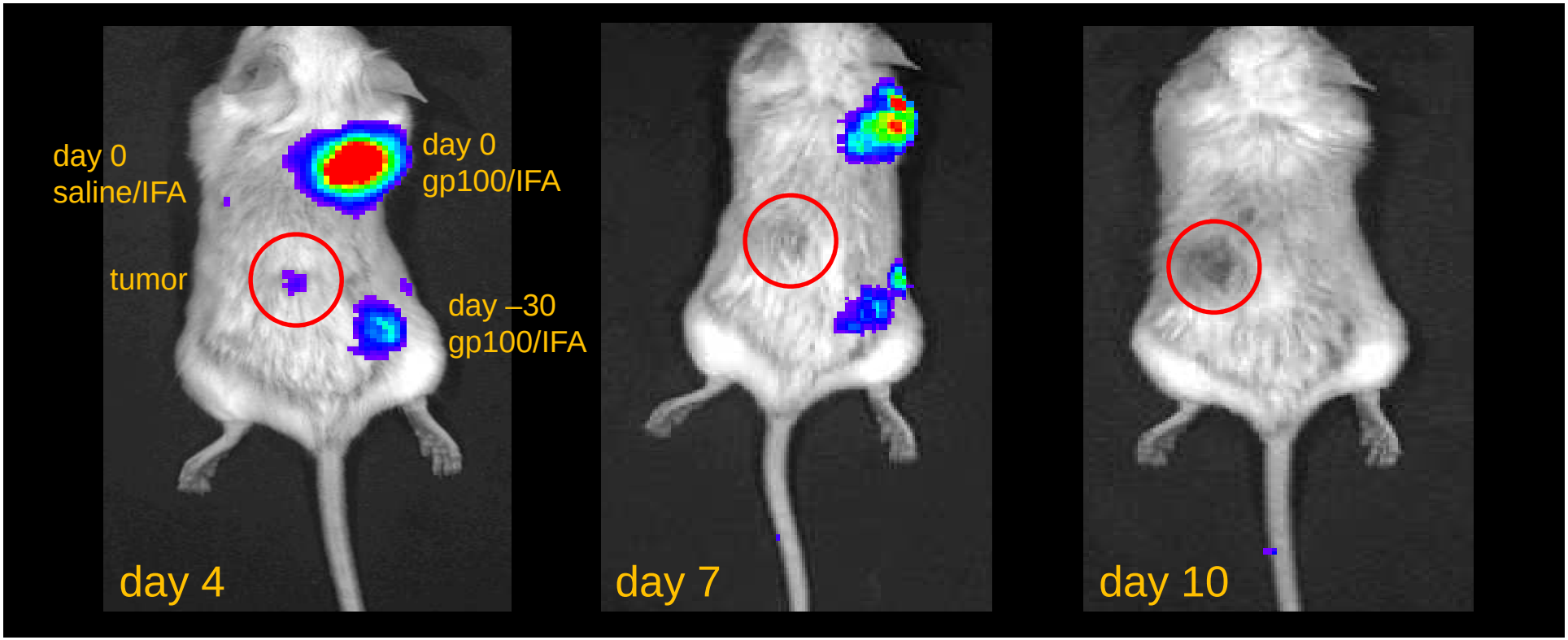


Hiep Khong

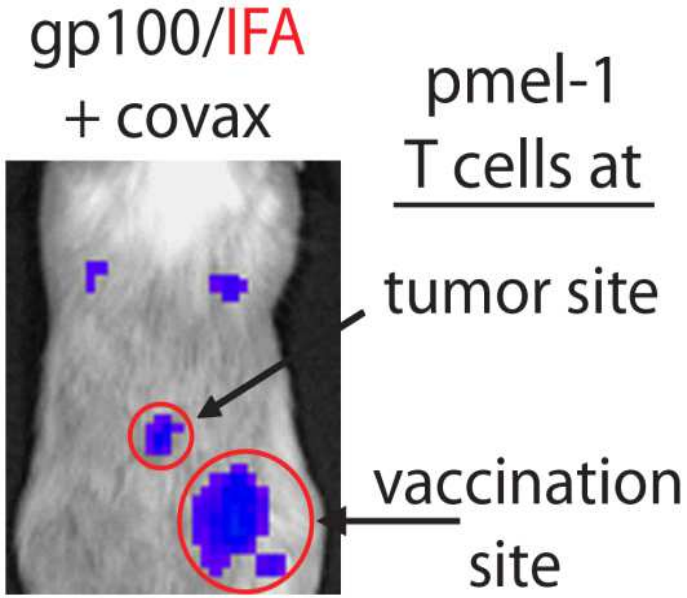
Where are the T cells?

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

Rabinovich *et al.*, PNAS 2008

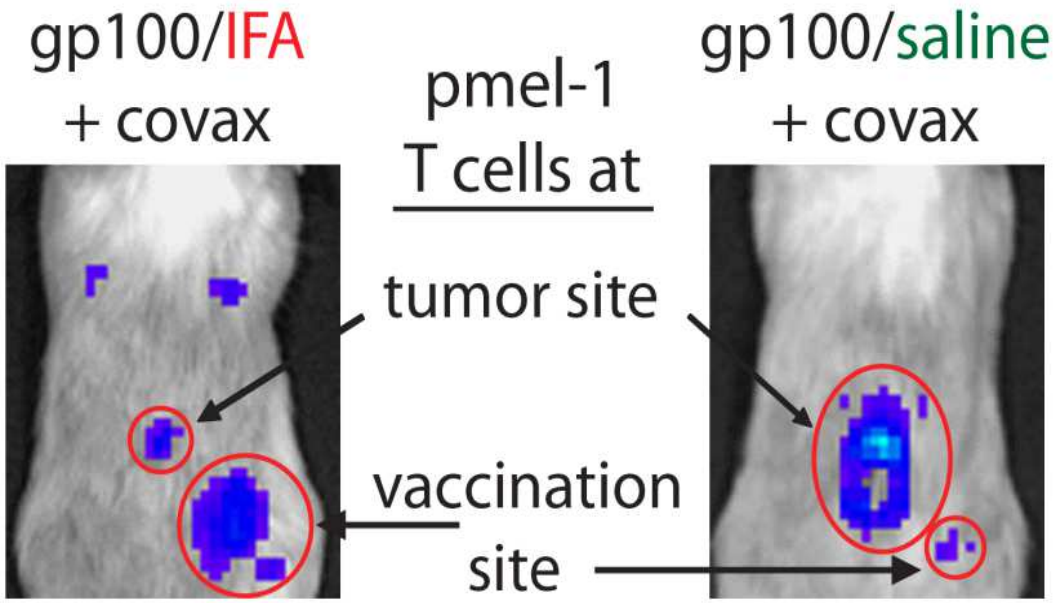


Oil-based vaccines sequester T cells at the vaccination site



Hailemichael *et al*., Nat. Med. 13, 2013

Water-based vaccines permit T cell accumulation in tumor



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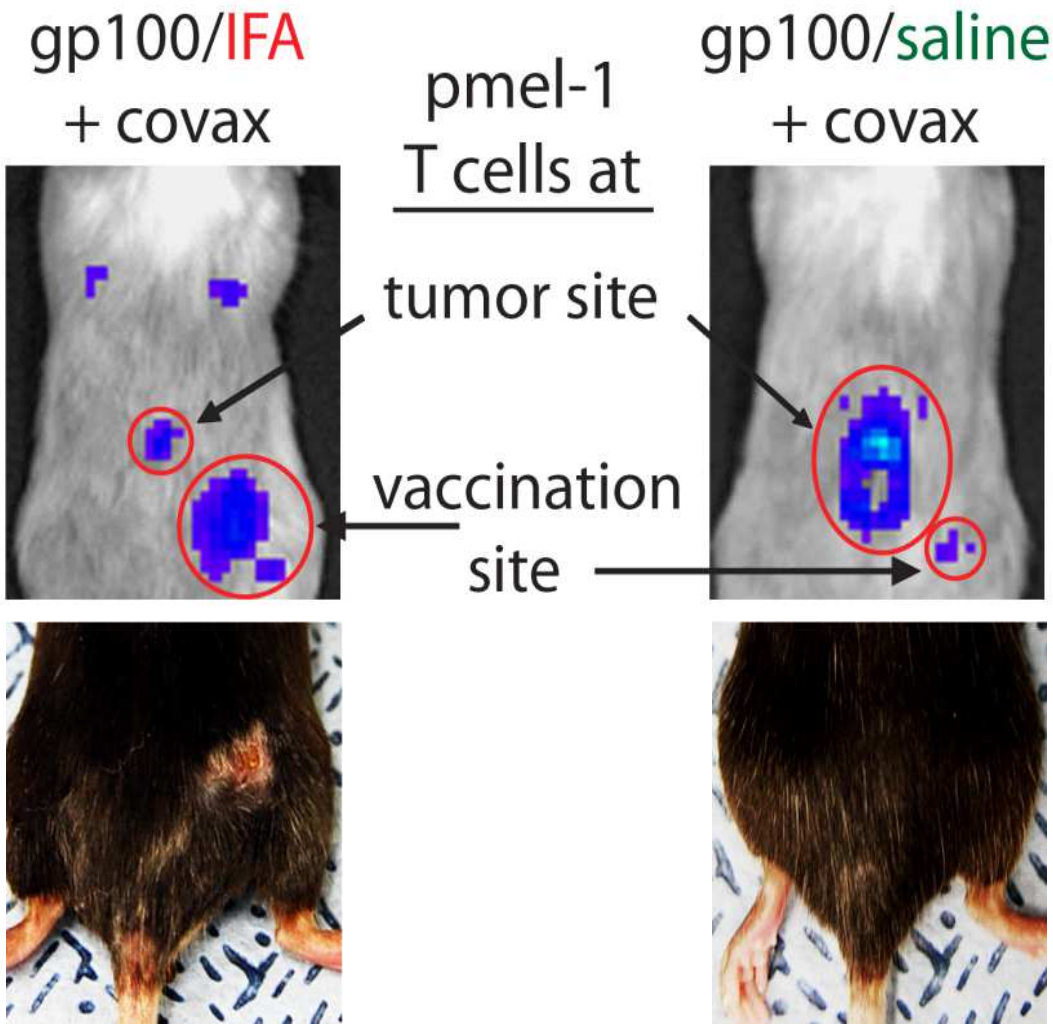
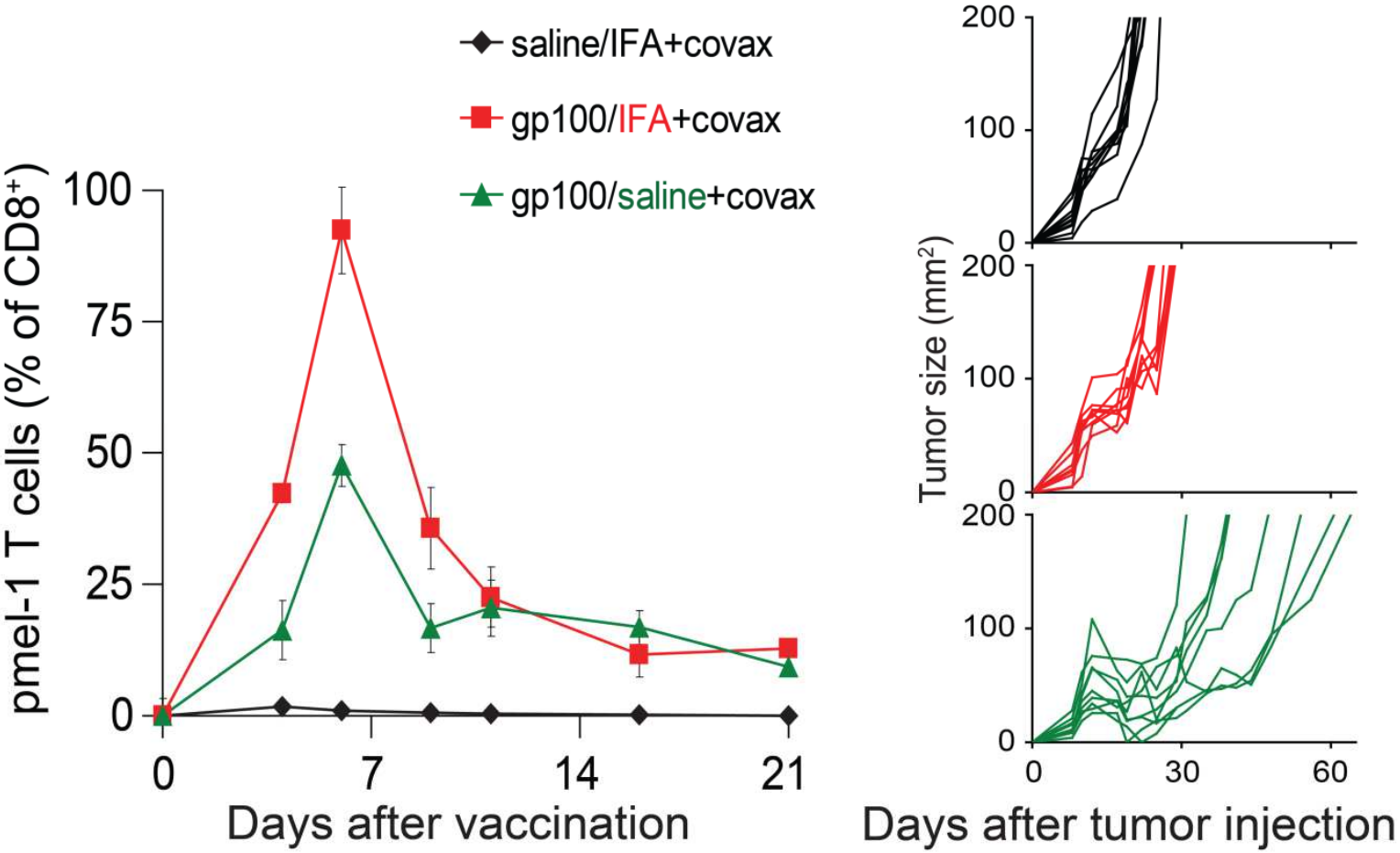


Hailemichael *et al*., Nat. Med. 13, 2013

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



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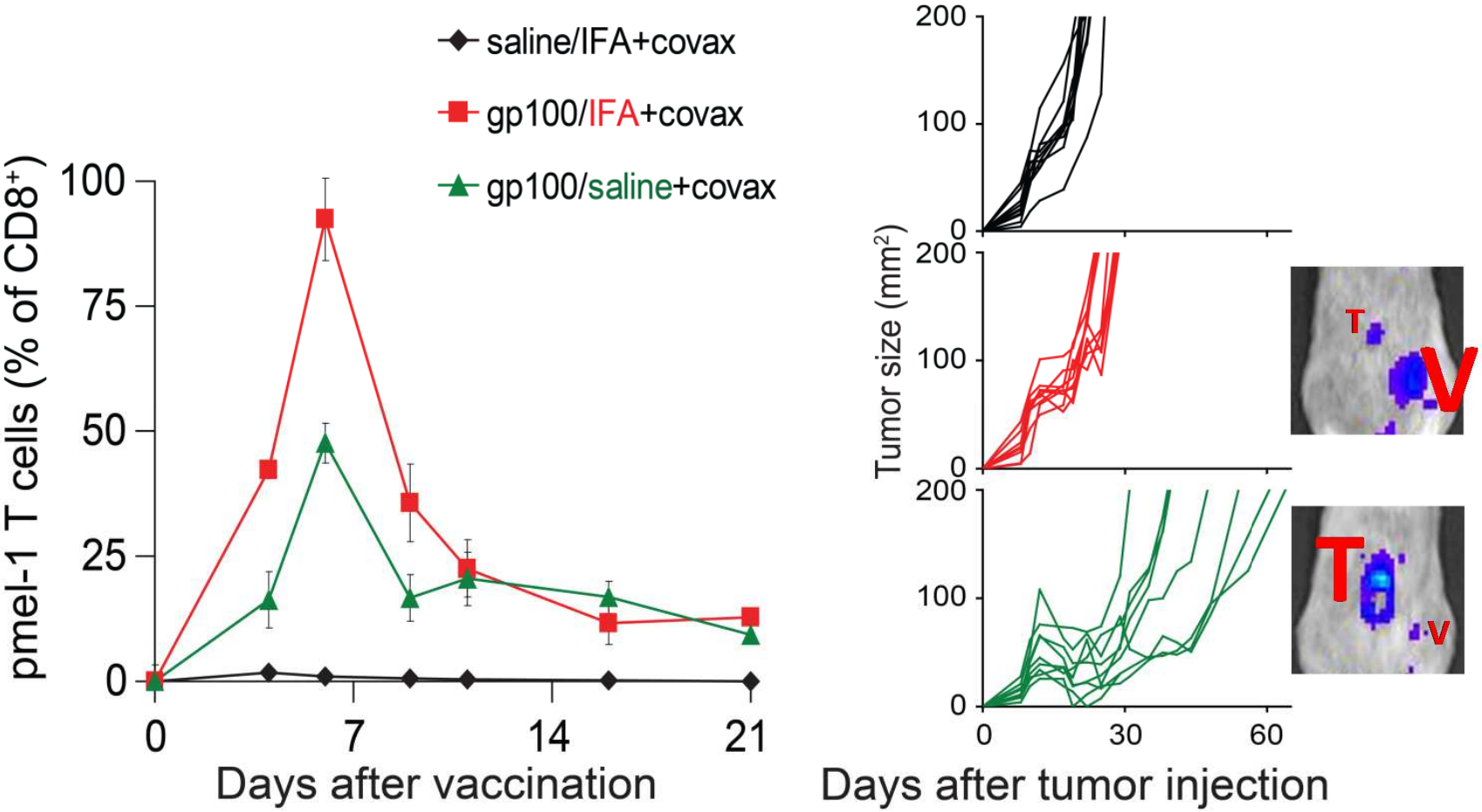

Hailemichael *et al*., Nat. Med. 13, 2013

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

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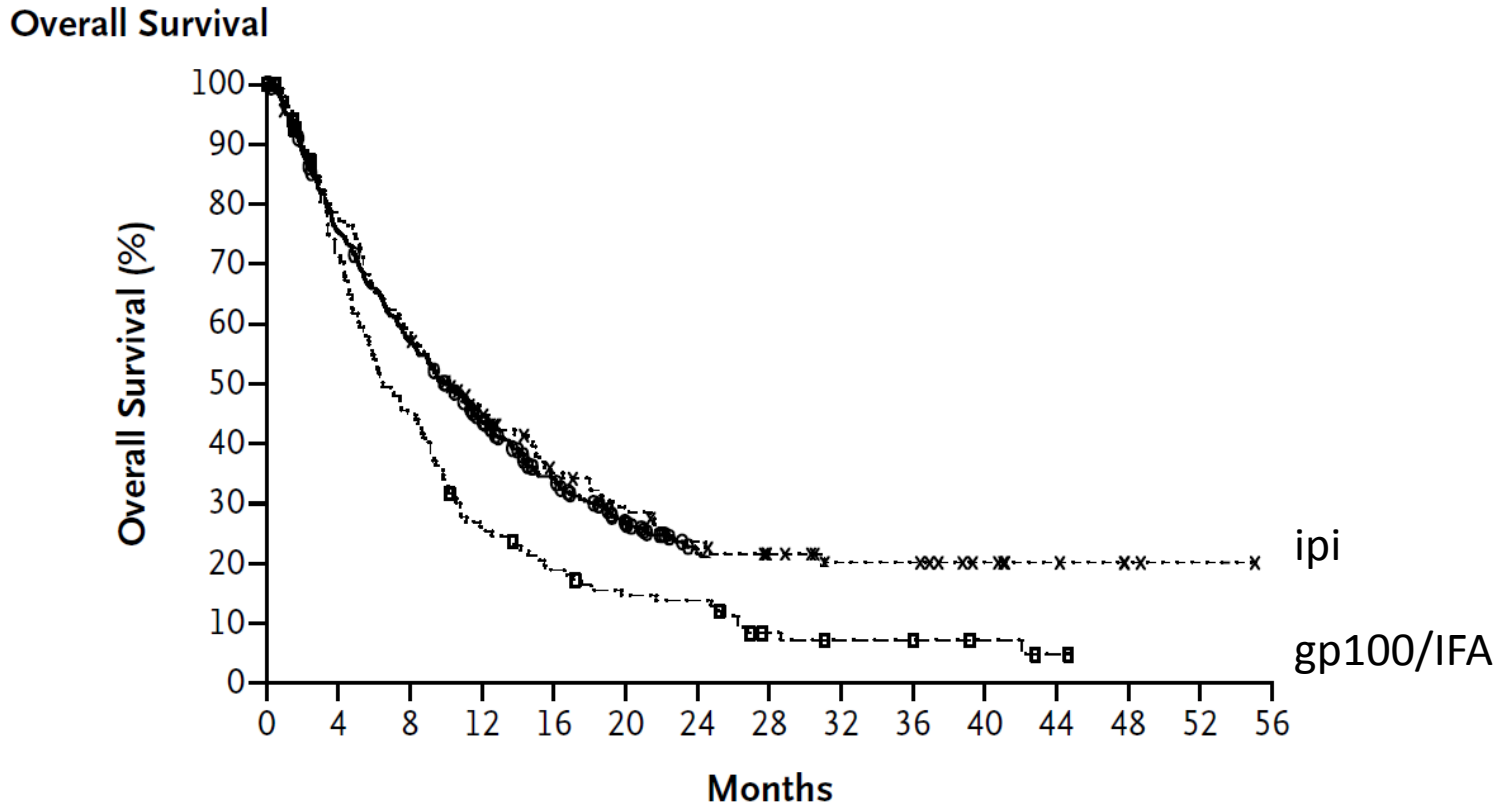
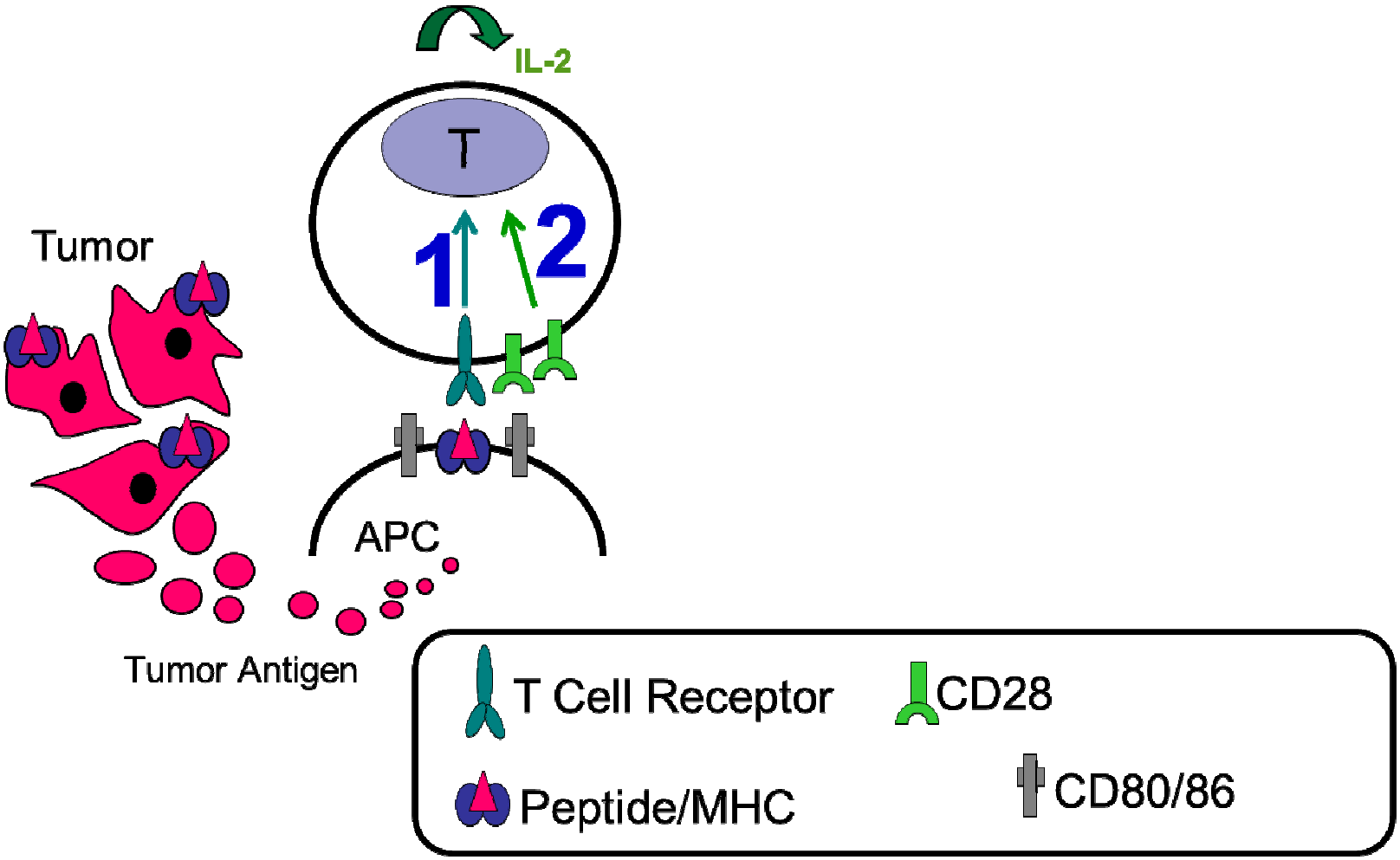
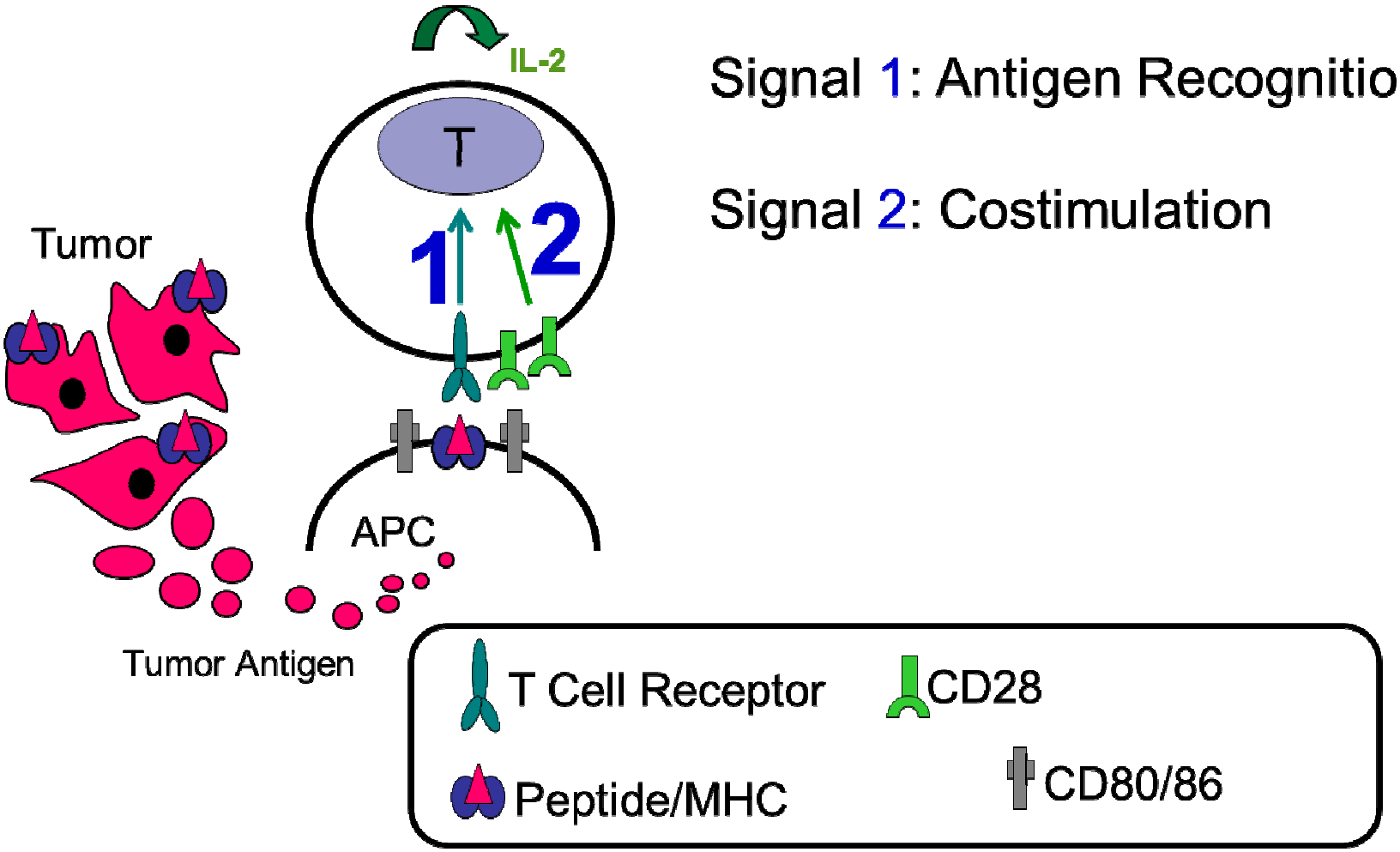


T cell Activation: 2 signals



adapted from JP Allison

T cell Activation: 2 signals

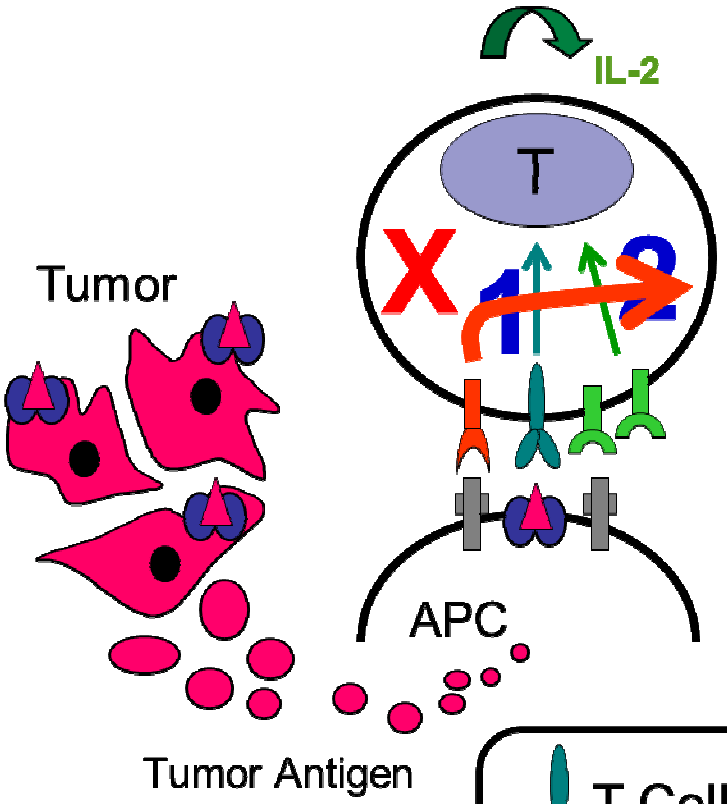


Signal 1: Antigen Recognition

Signal 2: Costimulation

adapted from JP Allison

T cell Activation: 2 signals



Signal 1: Antigen Recognition

Signal 2: Costimulation

Signal X: Checkpoint

T Cell Receptor

CD28

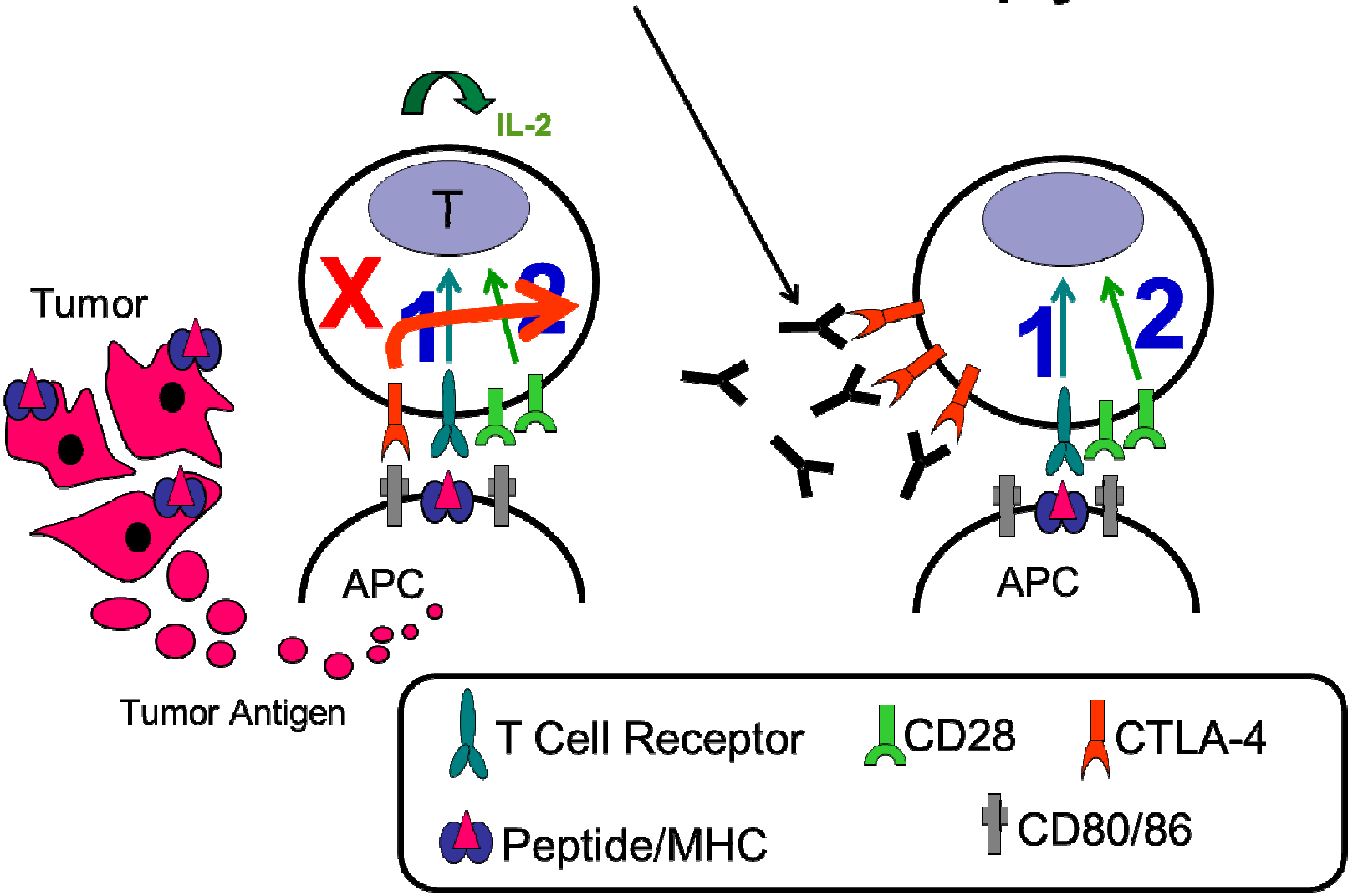
CTLA-4

Peptide/MHC

CD80/86

adapted from JP Allison

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.

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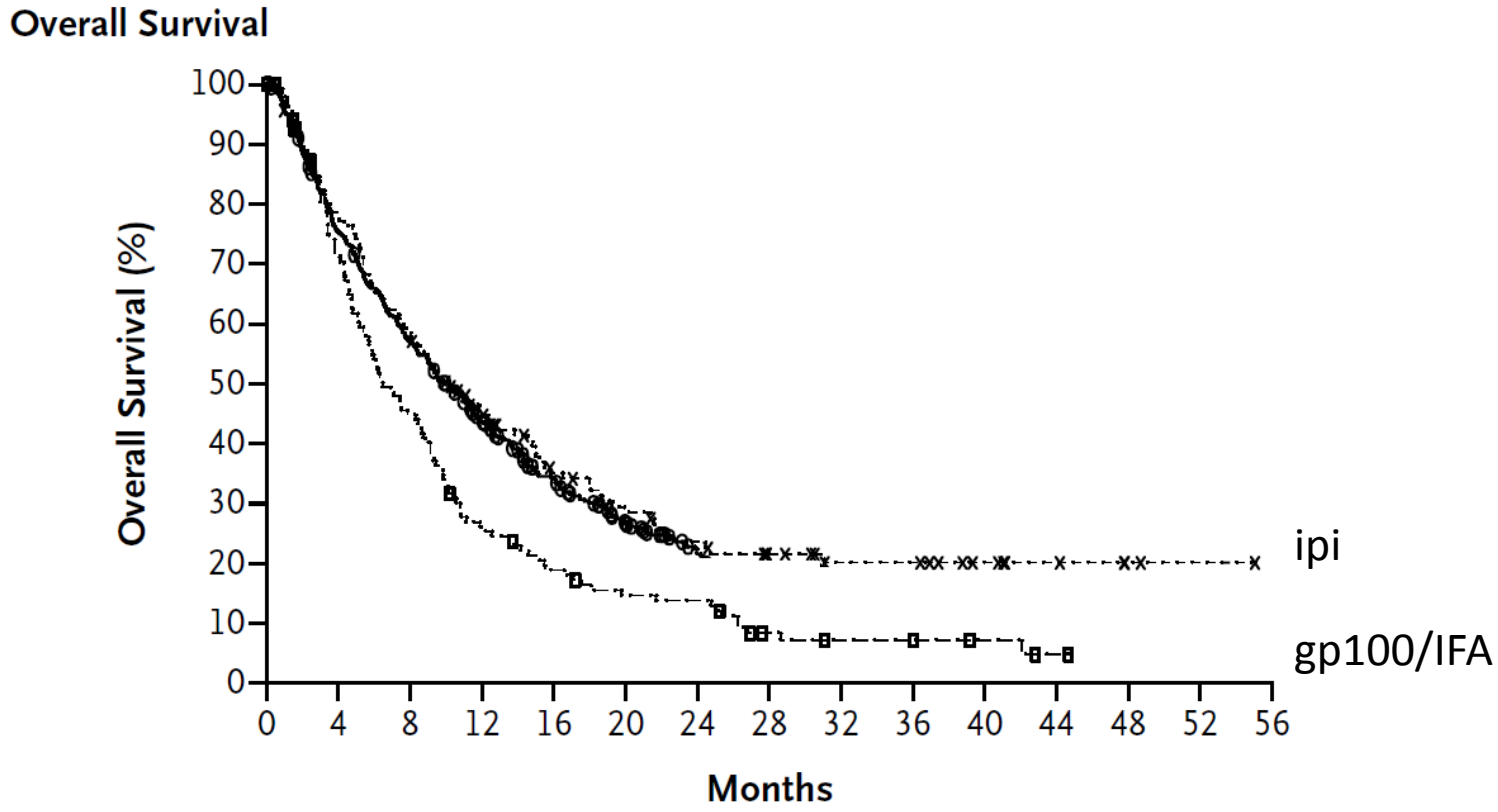

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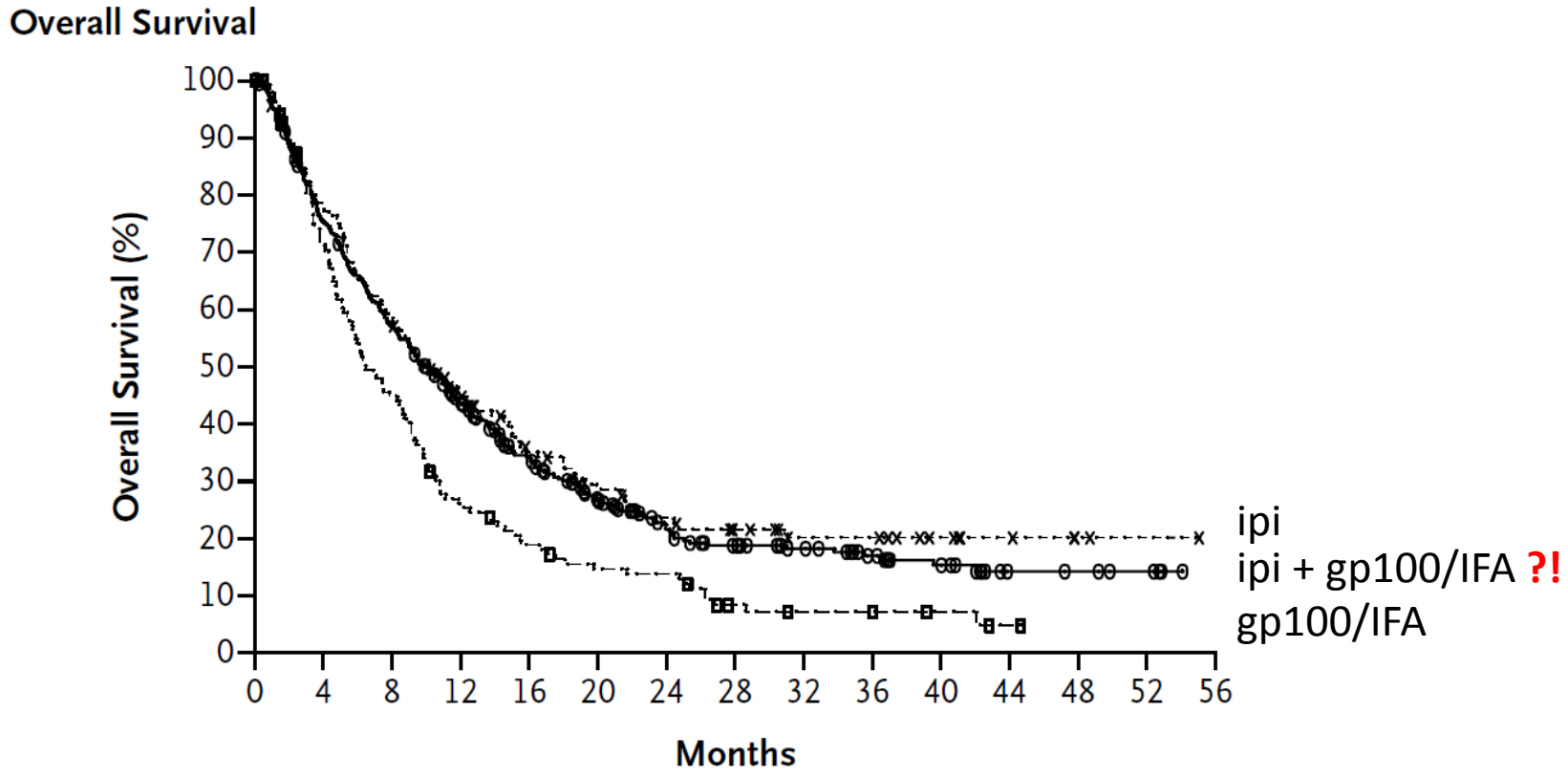
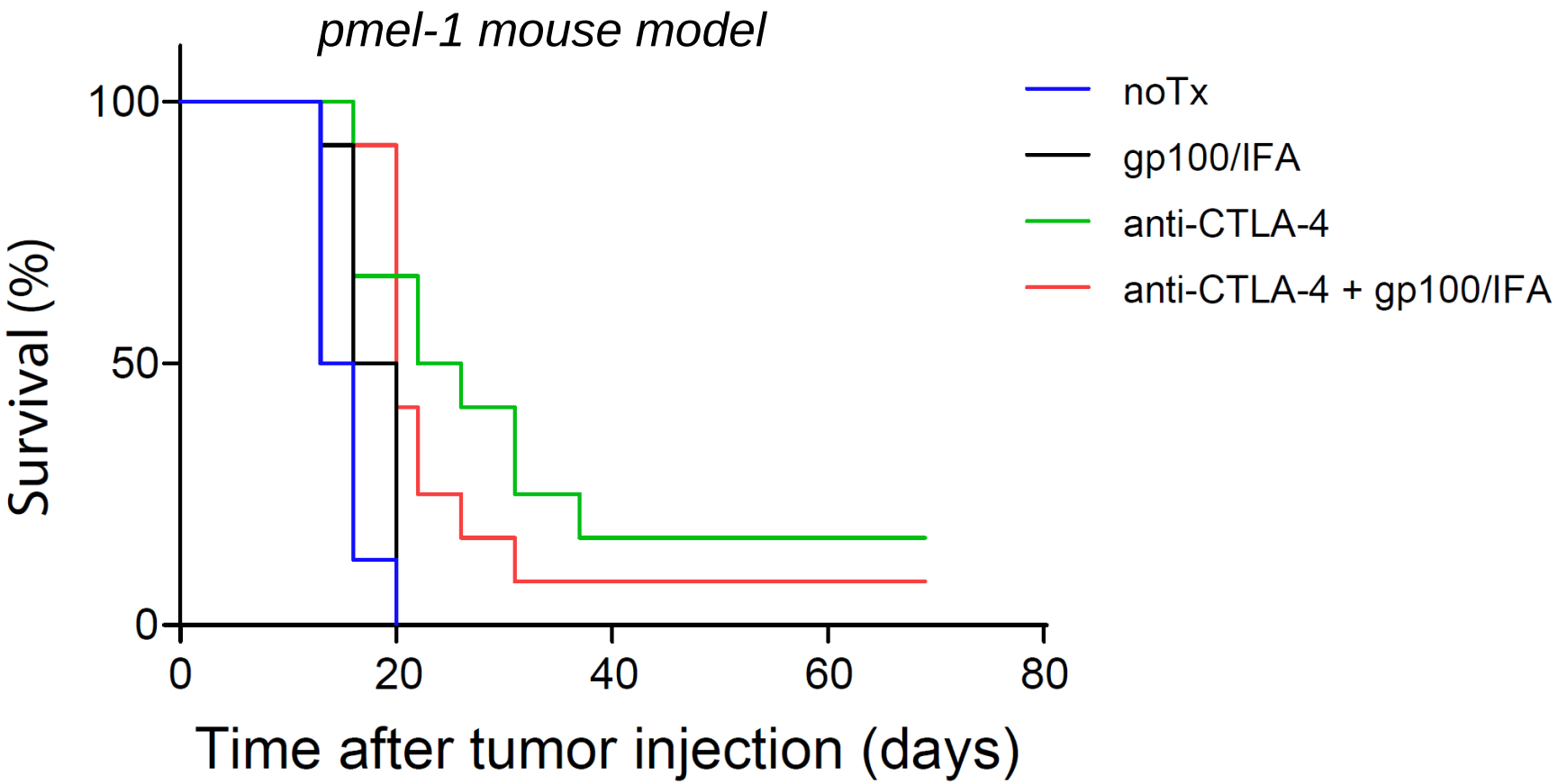
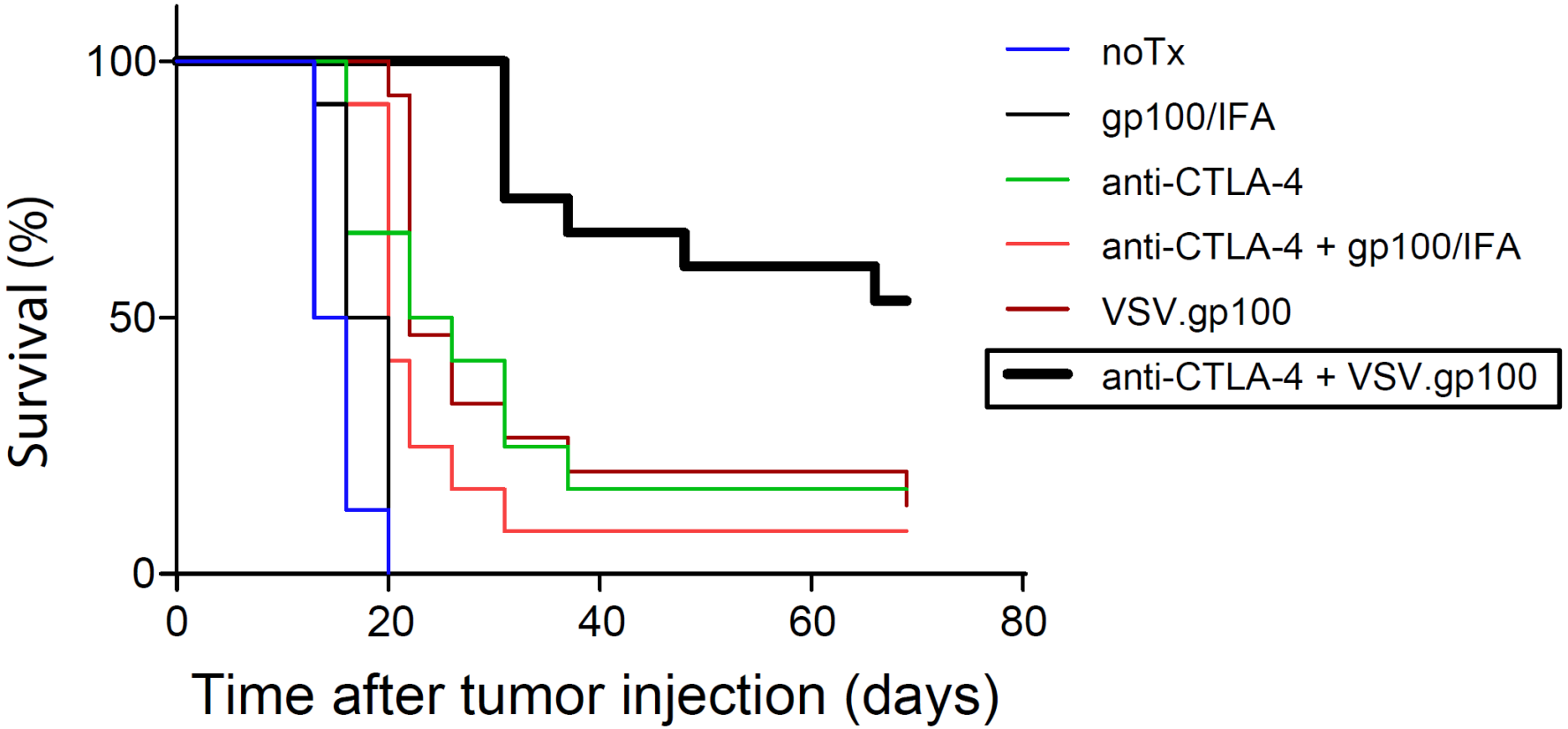


IFA-based vaccination does not synergize with anti-CTLA-4 therapy



Yared Hailemichael

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



Yared Hailemichael

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

Cancer Vaccine Laboratory
Dpt. of Melanoma Medical Oncology
Hiep Khong
Zhimin Dai, M.D.
Yared Hailemichael, Ph.D.
Manisha Singh, Ph.D.
Zhilan Xiao, M.D.
Meenu Sharma, Ph.D.
Derek Moore, M.D.

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