Cancer Vaccines

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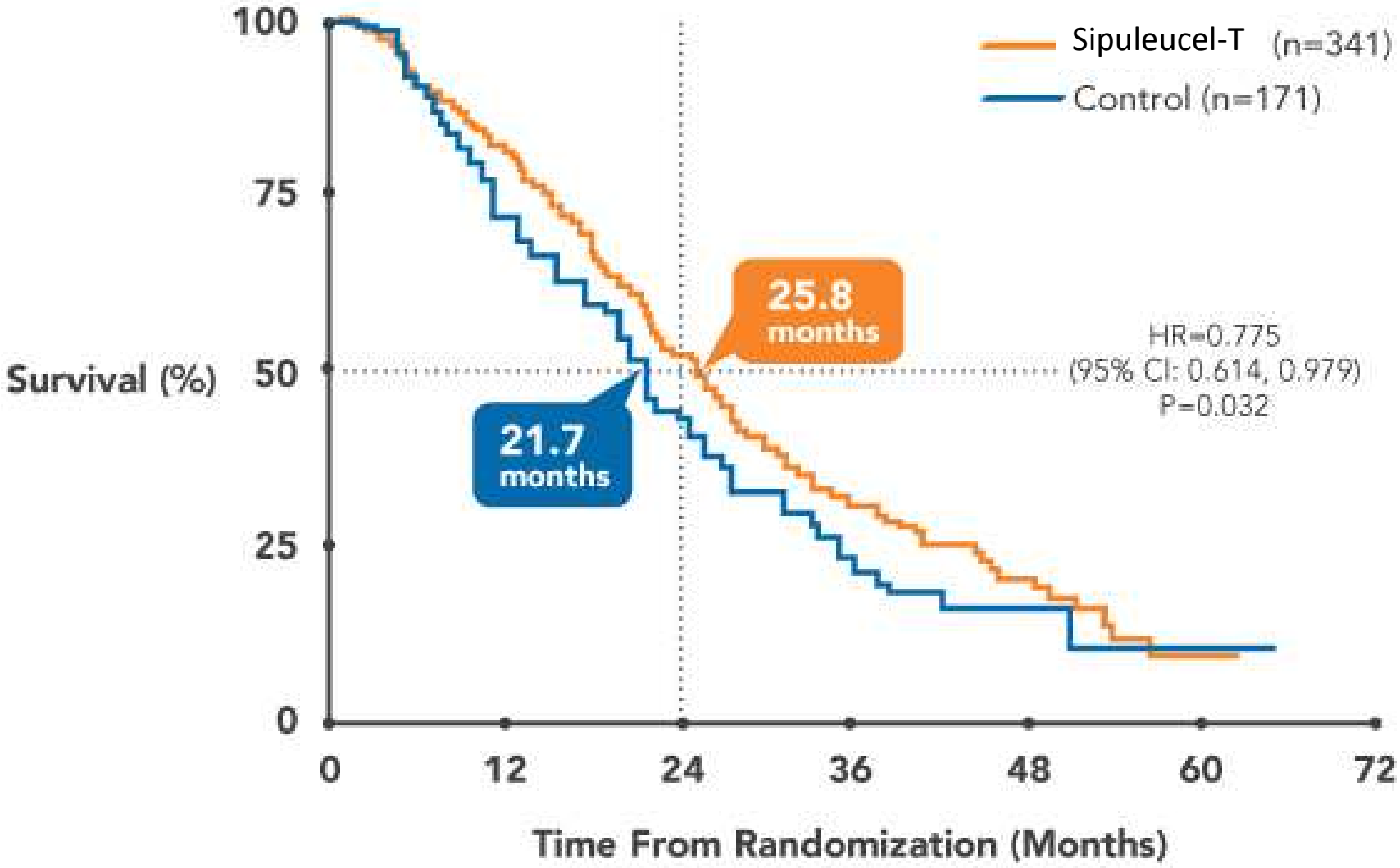
THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

What is a Cancer Vaccine?

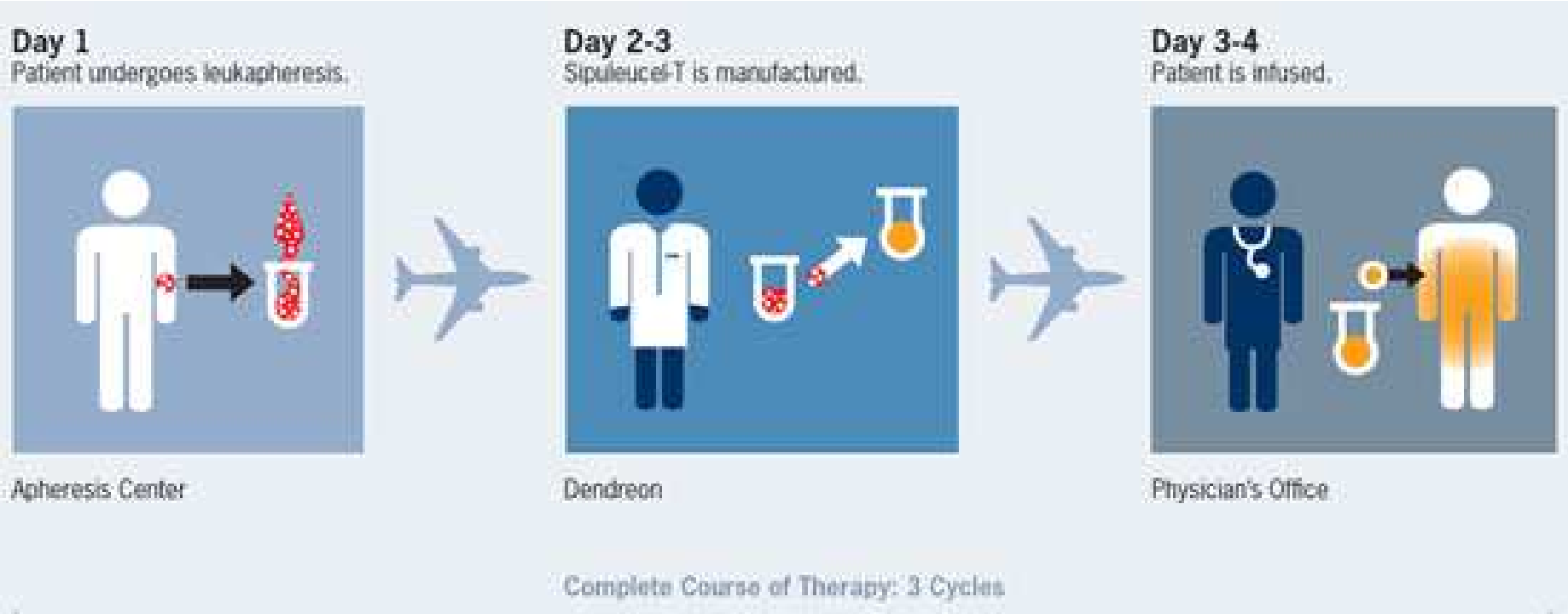
A preparation of a tumor antigen (usually protein) that upon administration stimulates antibody production or cellular anti-tumor immunity.

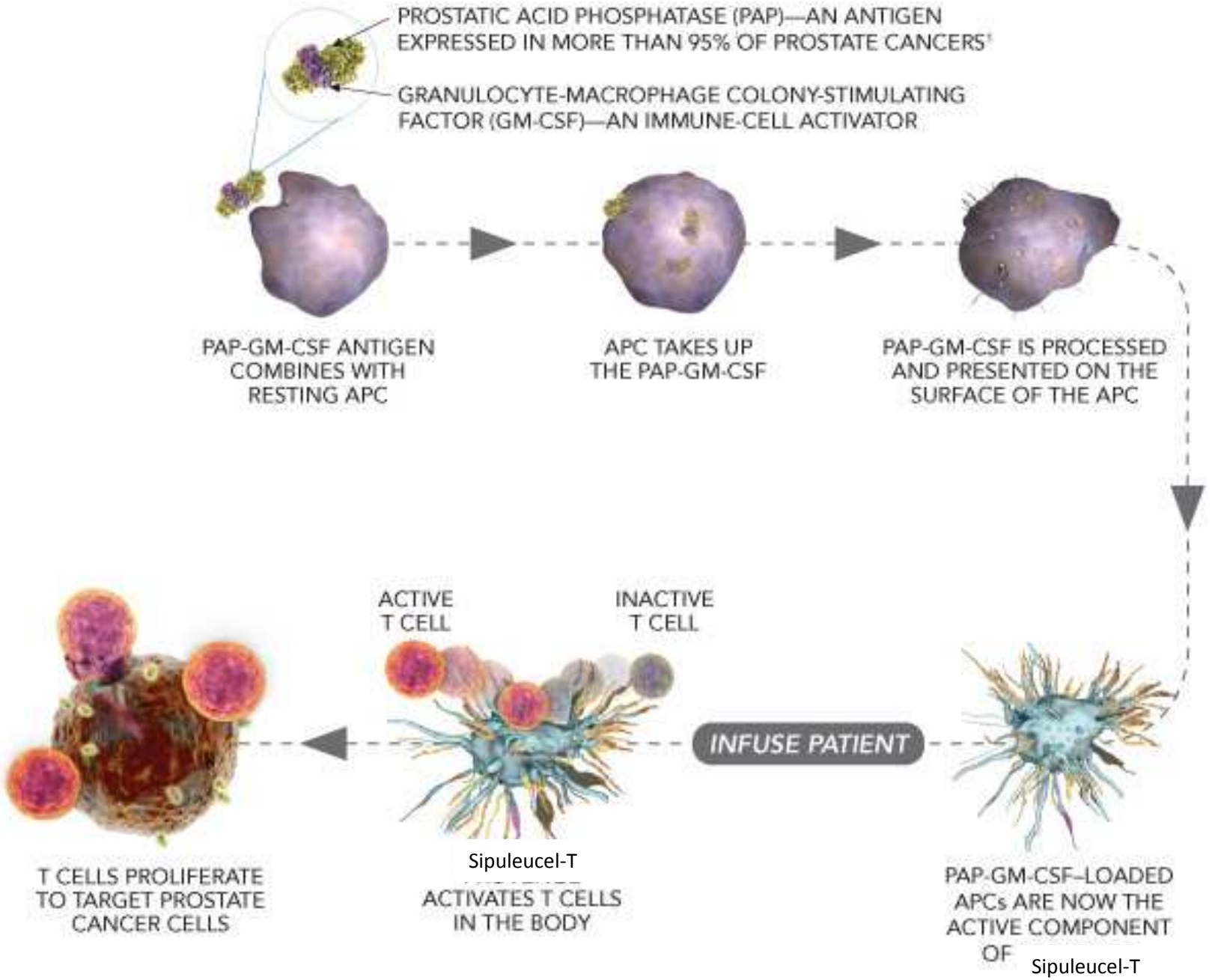
Sipuleucel-T for Prostate Cancer

FDA-approved April, 2010



Sipuleucel-T for Prostate Cancer




PROSTATIC ACID PHOSPHATASE (PAP)—AN ANTIGEN EXPRESSED IN MORE THAN 95% OF PROSTATE CANCERS[1]
GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR (GM-CSF)—AN IMMUNE-CELL ACTIVATOR
PAP-GM-CSF ANTIGEN COMBINES WITH RESTING APC
APC TAKES UP THE PAP-GM-CSF
PAP-GM-CSF IS PROCESSED AND PRESENTED ON THE SURFACE OF THE APC
ACTIVE T CELL
INACTIVE T CELL
INFUSE PATIENT
T CELLS PROLIFERATE TO TARGET PROSTATE CANCER CELLS
Sipuleucel-T
ACTIVATES T CELLS IN THE BODY
PAP-GM-CSF–LOADED APCs ARE NOW THE ACTIVE COMPONENT OF
Sipuleucel-T

nature medicine

PERSPECTIVE

VOLUME 10 | NUMBER 9 | SEPTEMBER 2004

Cancer immunotherapy: moving beyond current vaccines

Steven A Rosenberg, James C Yang & Nicholas P Restifo

35 clinical trials

765 patients

objective response rate = **3.8%**

What is a Cancer Vaccine?

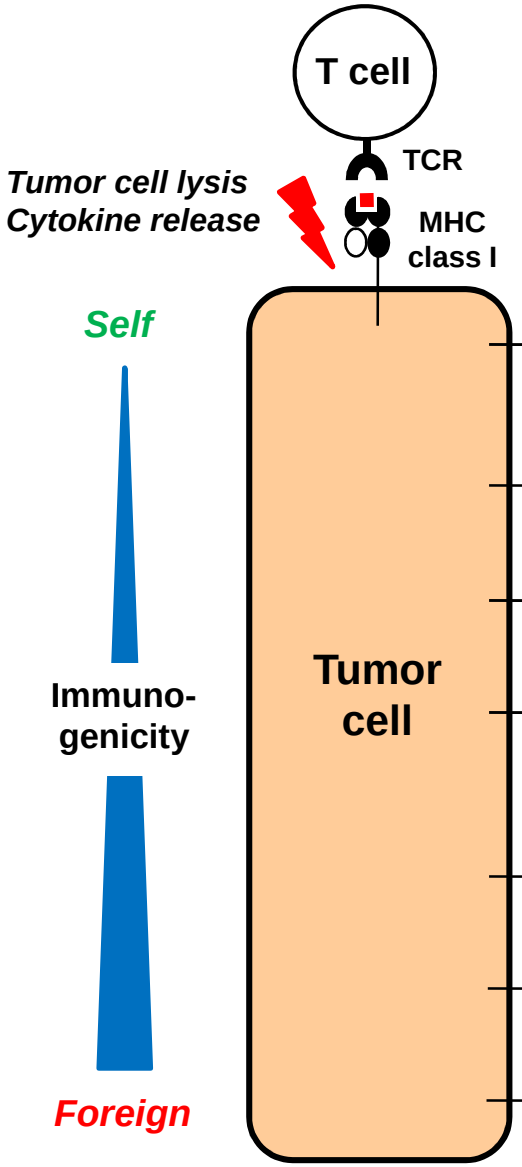
A **preparation** of a **tumor antigen** (usually protein) that upon administration stimulates antibody production or cellular anti-tumor immunity.

What is a Cancer Vaccine?

peptide(s)

A **preparation** of a **tumor antigen** (usually protein) that upon administration stimulates antibody production or cellular anti-tumor immunity.

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)**

→ **Single point mutations**

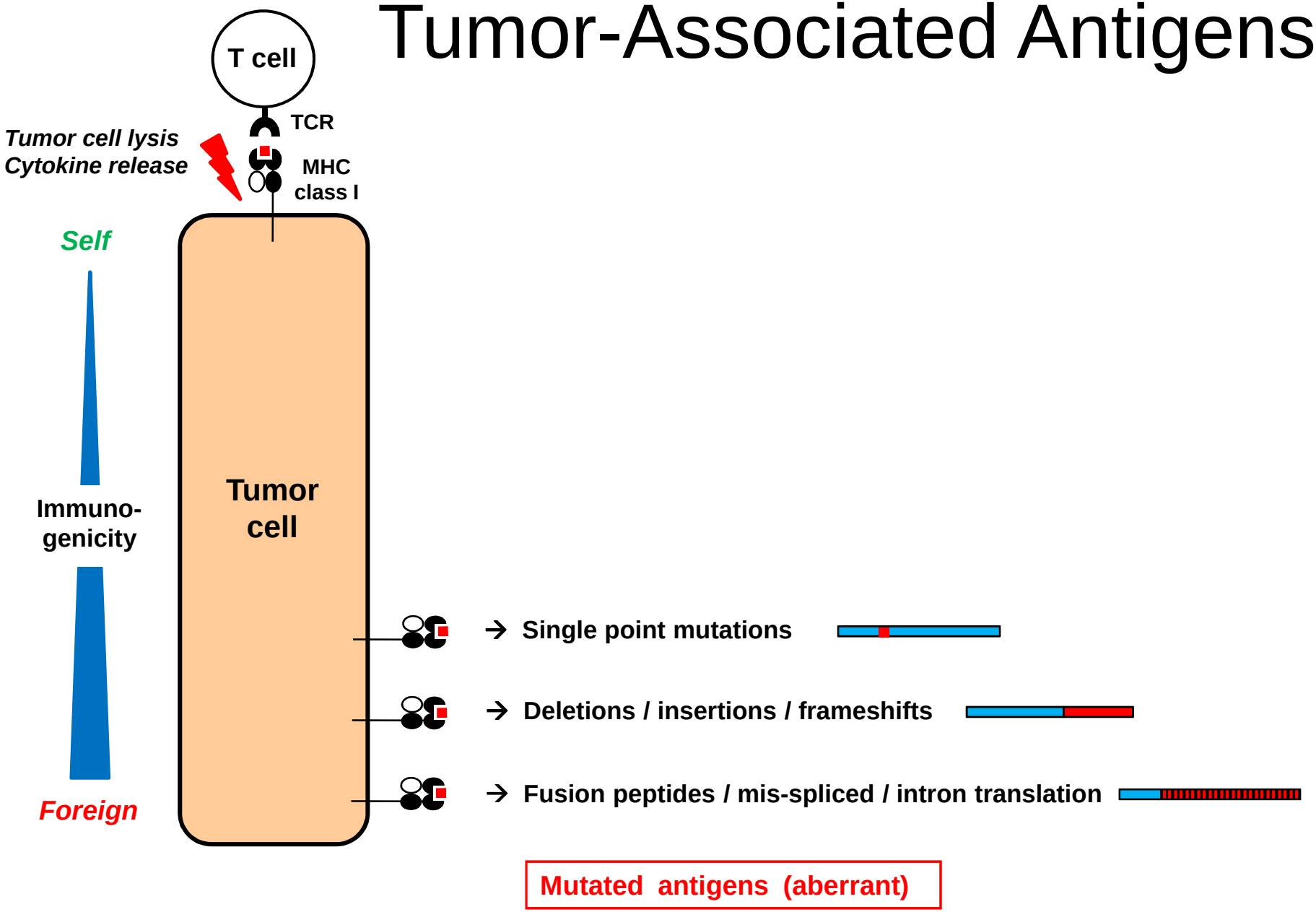
→ **Deletions / insertions / frameshifts**

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

Mutated antigens (aberrant)

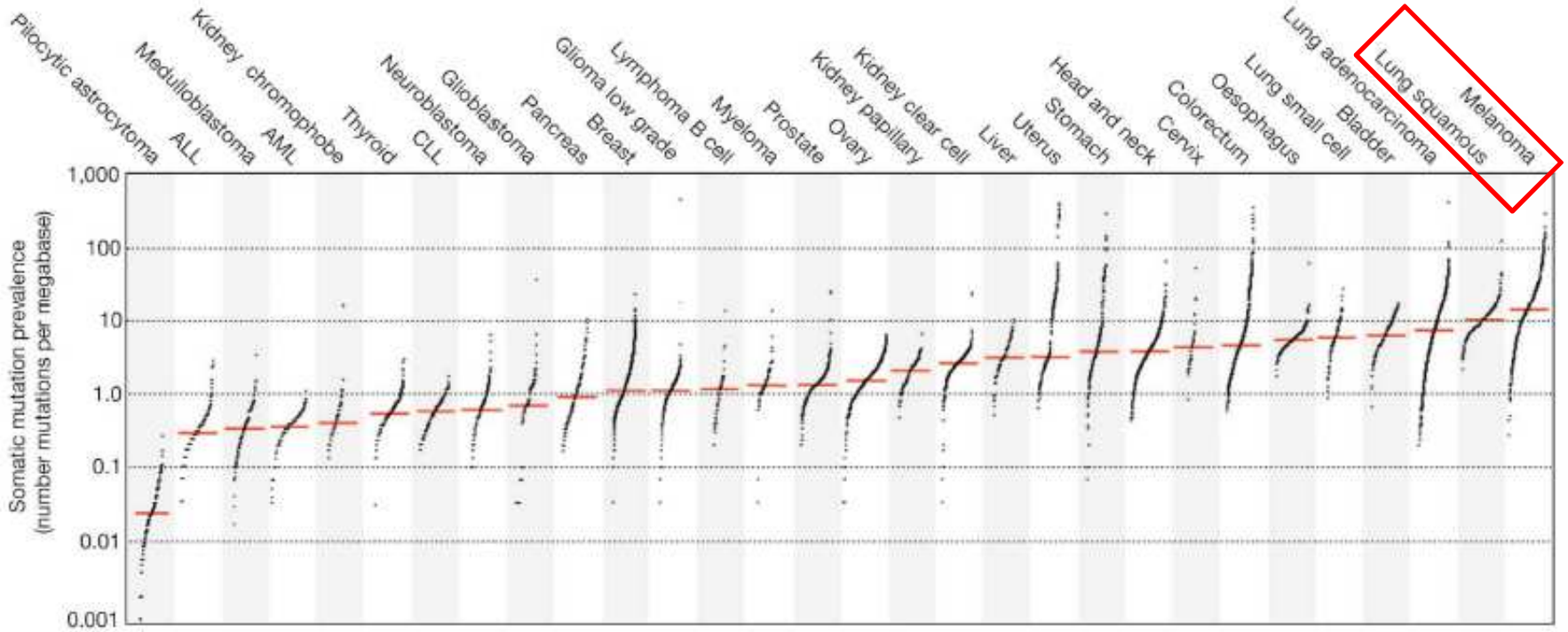
Adapted from Dr. Gregory Lizee, Melanoma Med. Oncol.

Tumor-Associated Antigens



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

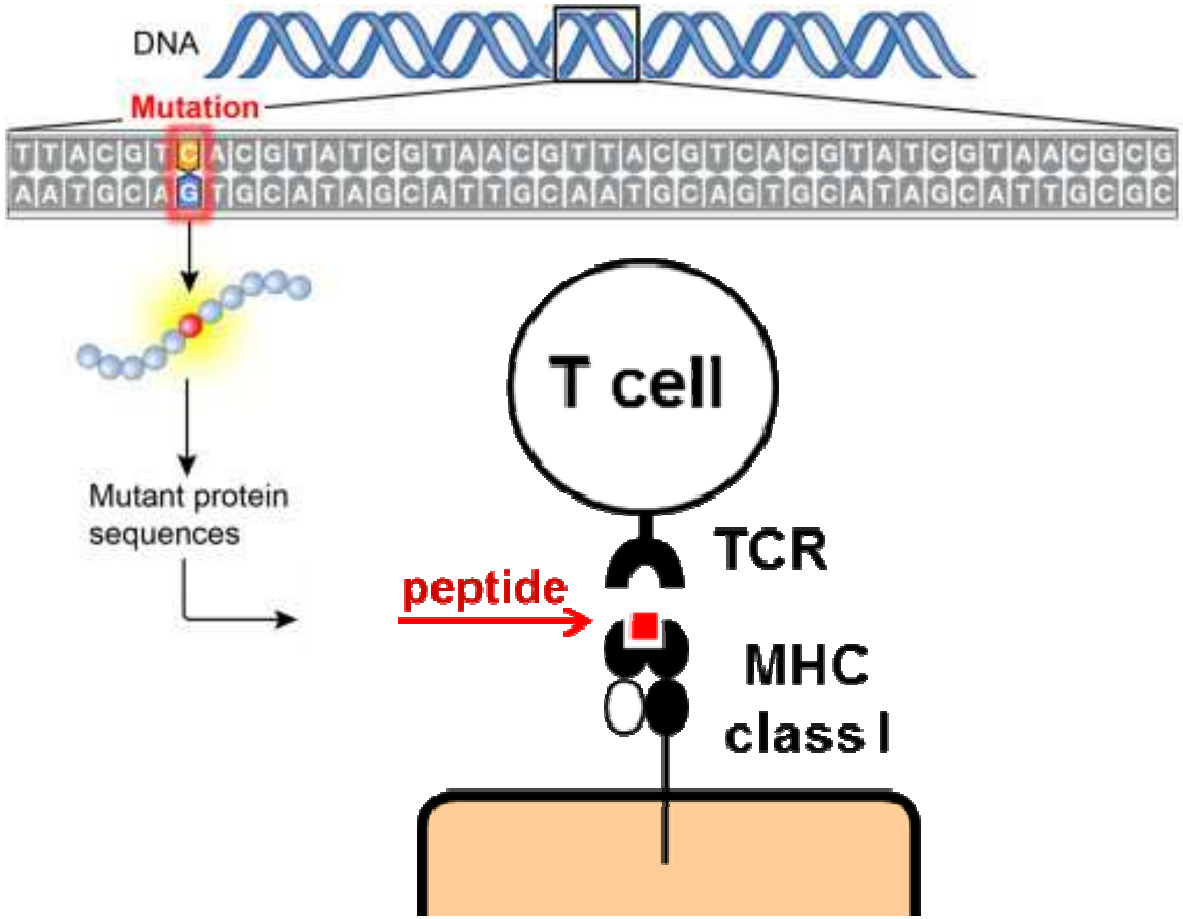
The prevalence of somatic mutations across human cancer types



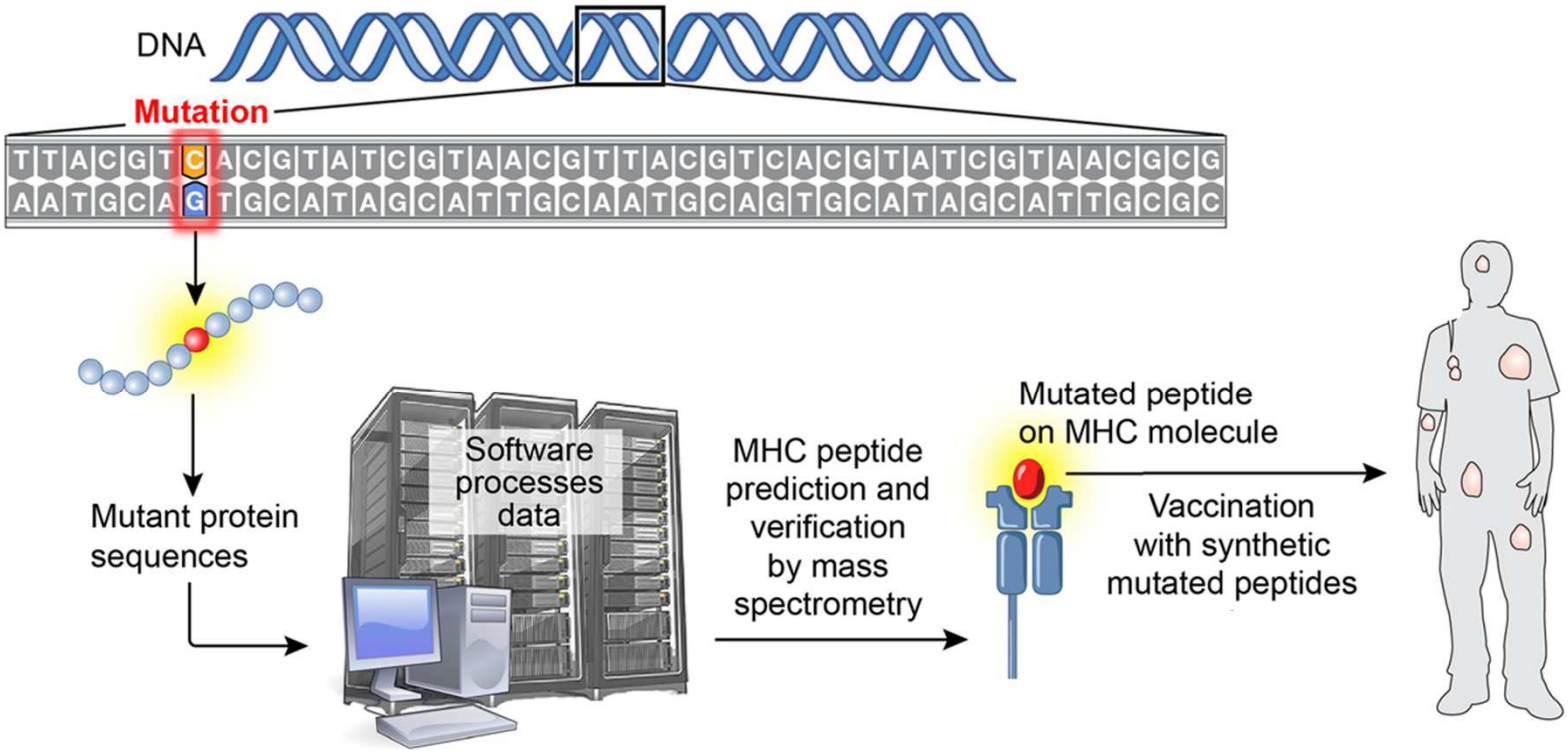
Signatures of mutational processes in human cancer Alexandrov et al.

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

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 antibody production or cellular anti-tumor immunity.

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

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

Question

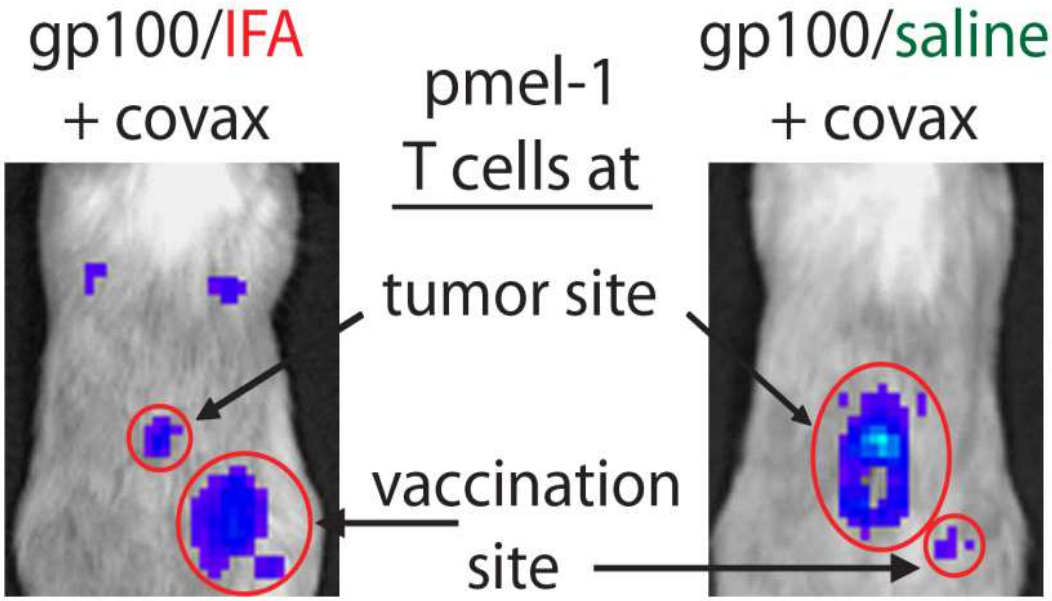
Why do many vaccinated cancer patients not experience tumor regression despite increased levels of cancer-specific T cells?

Question

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

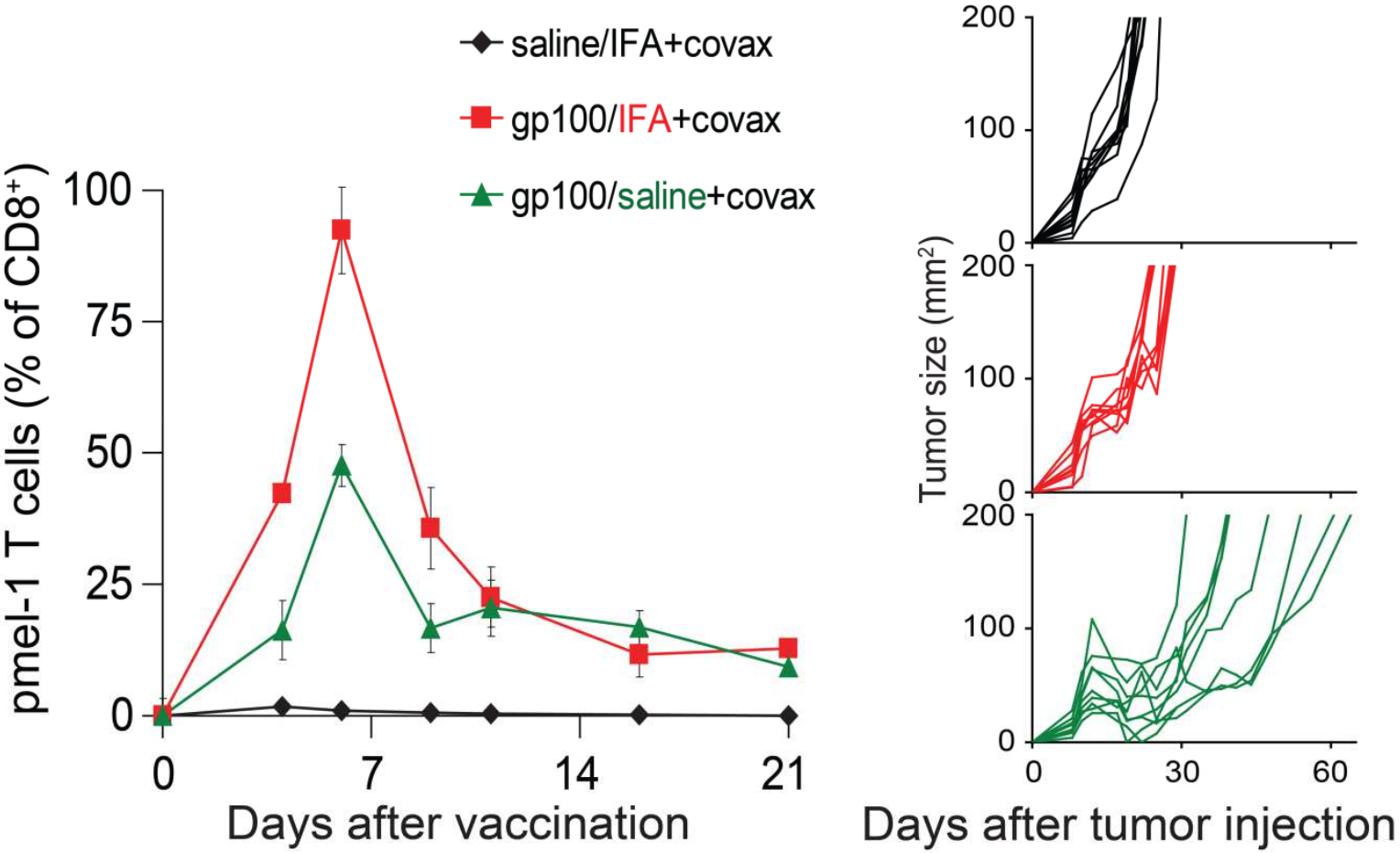
- immunosuppressive tumor microenvironment
- too few T cells induced
- poor T cell effector function/wrong phenotype
- poor T cell trafficking to tumor

Water-based vaccines permit T cell accumulation in tumor



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

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



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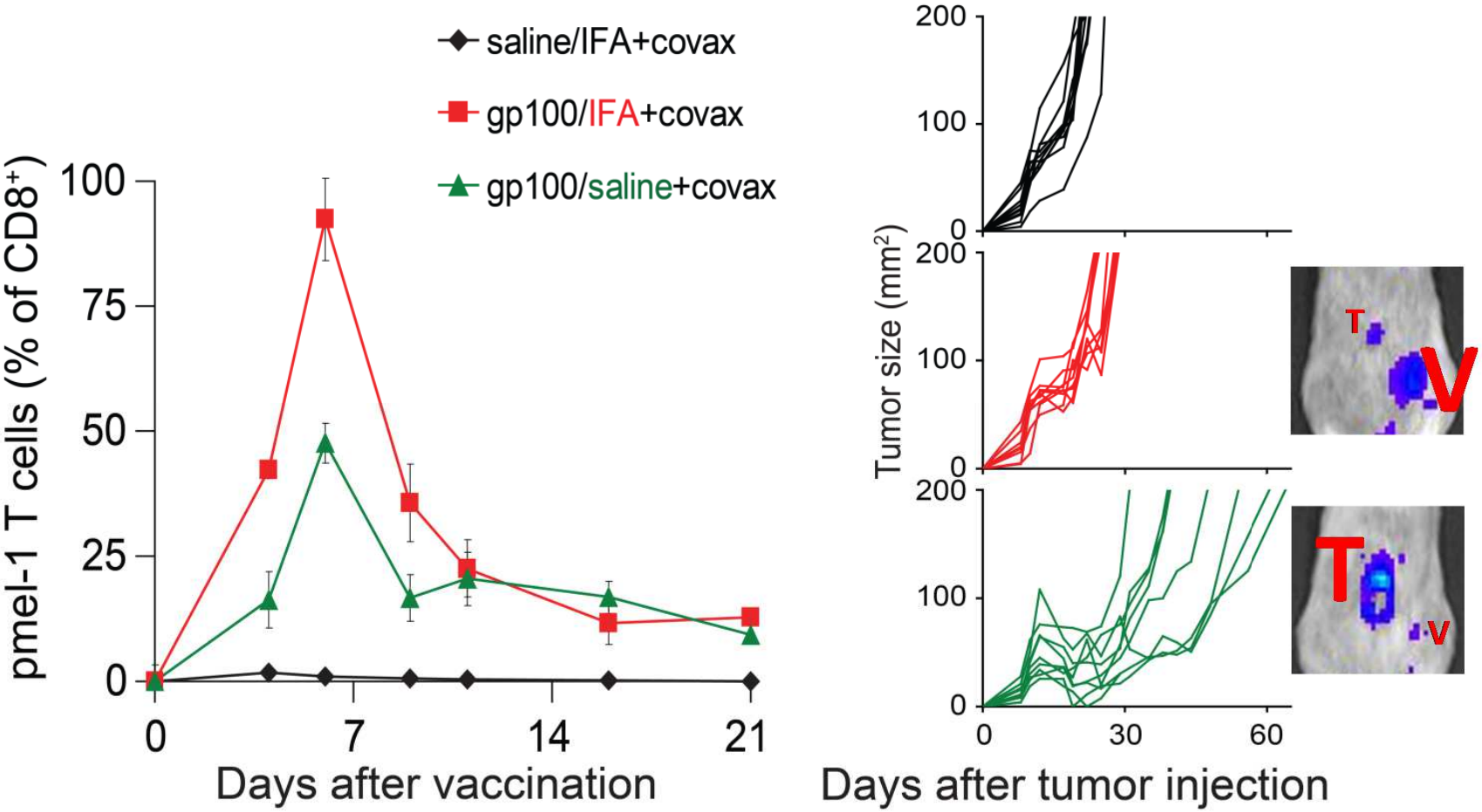


Hailemichael *et al*., Nat. Med. 13, 2013

Vaccines Based on Long Peptides Allow Better T Cell Trafficking

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)

Adjuvants remain underdeveloped

MAGE-A3 Cancer Immunotherapeutic Phase 3 Study in Melanoma Misses First Co-Primary Endpoint
(September 5, 2013)

Antigen: MAGE-A3 protein
Adjuvant: AS15 = liposomal QS-21 + MPL + CpG

Phase 3 randomized, blinded, placebo-controlled vaccine trial.

Outcome: no improved disease-free survival compared to placebo

Peptide vaccines can be enhanced with TLR agonists

Rapid and strong human CD8+ T cell responses to vaccination with peptide, IFA, and CpG oligodeoxynucleotide 7909

Daniel E. Speiser,[1] Danielle Liénard,[1,2] Nathalie Rufer,[3] Verena Rubio-Godoy,[1] Donata Rimoldi,[1] Ferdy Lejeune,[2] Arthur M. Krieg,[4] Jean-Charles Cerottini,[1,5] and Pedro Romero[1]

Adding CpG to vaccine boosted Melan-A/MART-1-specific CD8+ T cells responses in blood by 10-fold

J. Clin. Invest. **115**:739–746 (2005).

Peptide vaccines can be enhanced with TLR agonists

Phase I Trial of Overlapping Long Peptides from a Tumor Self-Antigen and Poly-ICLC Shows Rapid Induction of Integrated Immune Response in Ovarian Cancer Patients

Paul Sabbatini, Takemasa Tsuji, Luis Ferran, et al.

Adding Poly-ICLC (TLR 3 agonist) to NY-ESO-1 peptides in IFA increased specific antibody and T cell responses

Clin Cancer Res 2012;18:6497-6508

Peptide vaccines can be enhanced by reformulation

European Journal of Immunology

Nano-particle vaccination combined with TLR-7 and -9 ligands triggers memory and effector CD8+ T-cell responses in melanoma patients

Simone M. Goldinger[1], Reinhard Dummer[1], Petra Baumgaertner[2], Daniela Mihic-Probst[1], Katrin Schwarz[3], Anya Hammann-Haenni[3], Joerg Willers[3], Christine Geldhof[2], John O. Prior[2], Thomas M. Kündig[1], Olivier Michielin[2], Martin F. Bachmann[3] and Daniel E. Speiser[2]

A virus-like nanoparticle loaded with CpG-A and coupled to Melan-A/MART-1 peptide + topical imiquimod

GM-CSF as a peptide vaccine adjuvant

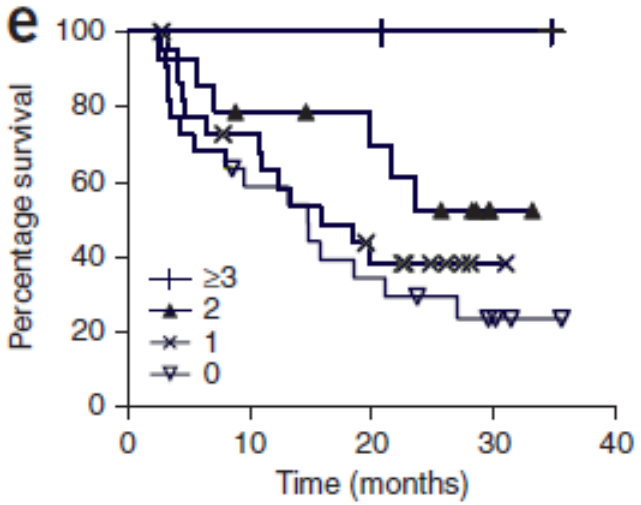
blood

1996 88: 202-210

Granulocyte-macrophage colony-stimulating factor: an effective adjuvant for protein and peptide-based vaccines

ML Disis, H Bernhard, FM Shiota, SL Hand, JR Gralow, ES Huseby, S Gillis and MA Cheever

GM-CSF as a peptide vaccine adjuvant



nature medicine AUGUST 2012

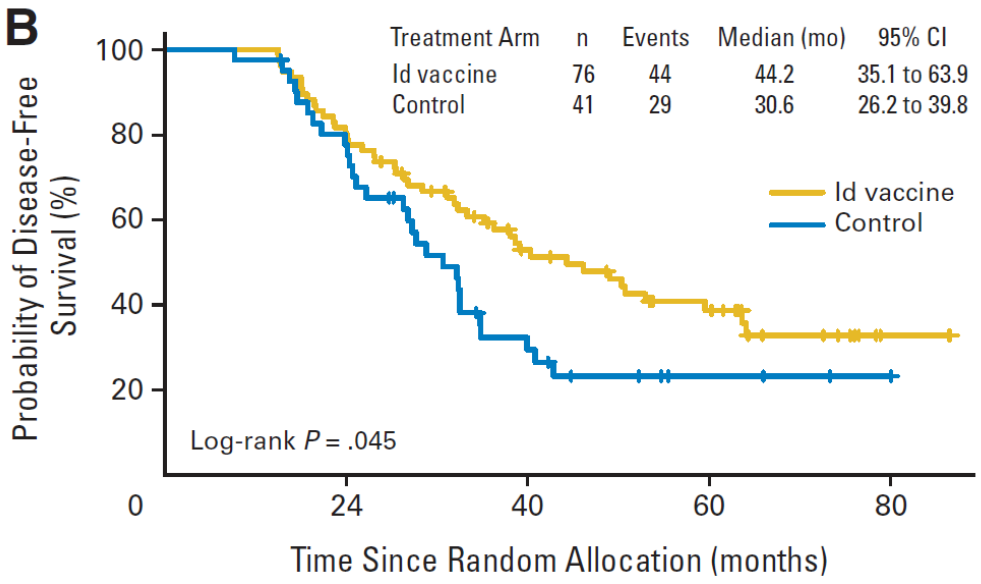
Multipeptide immune response to cancer vaccine IMA901 after single-dose cyclophosphamide associates with longer patient survival

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]

GM-CSF as a protein vaccine adjuvant

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

Effect of Granulocyte/Macrophage Colony-Stimulating Factor on Circulating $CD8^+$ and $CD4^+$ T-Cell Responses to a Multipeptide Melanoma Vaccine: Outcome of a Multicenter Randomized Trial

Craig L. Slingluff, Jr.,[1] Gina R. Petroni,[2] Walter C. Olson,[1] Mark E. Smolkin,[2] Merrick I. Ross,[4] Naomi B. Haas,[5] William W. Grosh,[3] Marc E. Boisvert,[6] John M. Kirkwood,[7] and Kimberly A. Chianese-Bullock[1]

Clin. Cancer Res. 2009

vaccine	% patients with CD8+ T cell response
12 mel. peptides + Tetanus helper	73
12 mel. peptides + Tetanus helper + GM-CSF	34 (?!)

Effect of Granulocyte/Macrophage Colony-Stimulating Factor on Circulating CD8+ and CD4+ T-Cell Responses to a Multipeptide Melanoma Vaccine: Outcome of a Multicenter Randomized Trial

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12 mel. peptides + Tetanus helper	73
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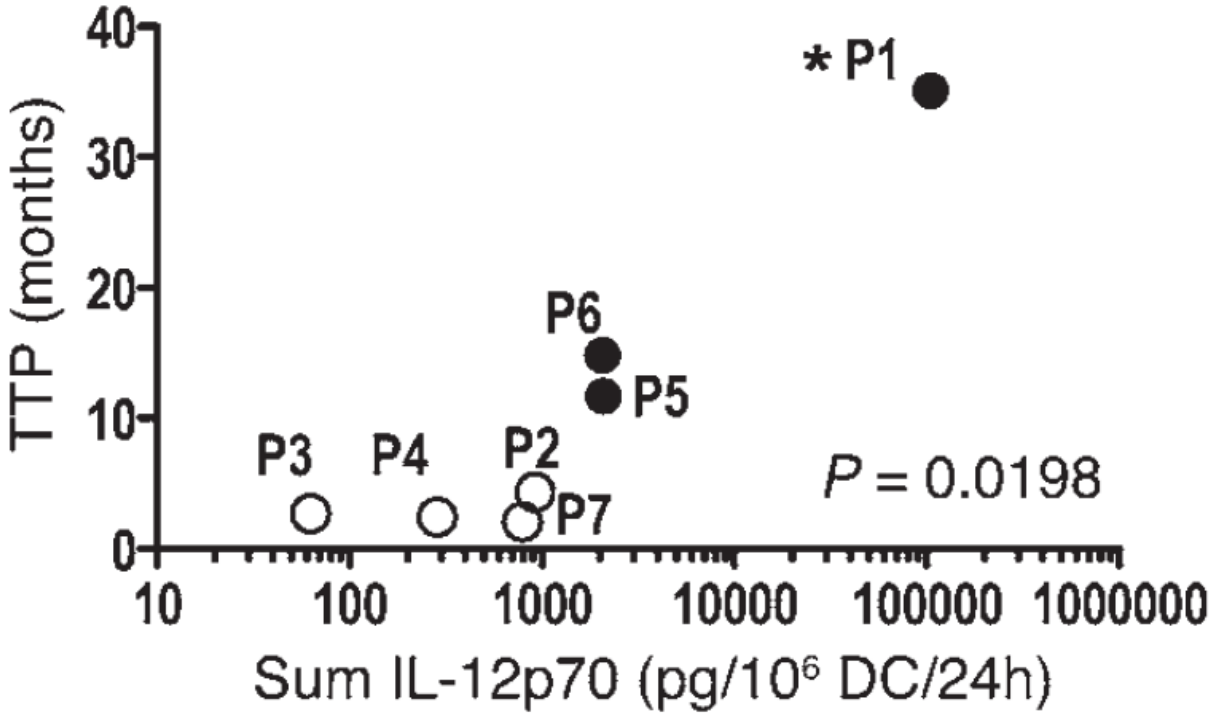
MFG-E8–mediated uptake of apoptotic cells by APCs links the pro- and antiinflammatory activities of GM-CSF

Masahisa Jinushi,[1,2] Yukoh Nakazaki,[1,2] Michael Dougan,[1,2] Daniel R. Carrasco,[1,2,3] Martin Mihm,[4] and Glenn Dranoff[1,2]

J. Clin. Invest., 2007

IL-12p70–producing patient DC vaccine elicits Tc1-polarized immunity

Beatriz M. Carreno,[1] Michelle Becker-Hapak,[1] Alexander Huang,[1] Megan Chan,[1] Amer Alyasiry,[1] Wen-Rong Lie,[2] Rebecca L. Aft,[3] Lynn A. Cornelius,[4] Kathryn M. Trinkaus,[5] and Gerald P. Linette[1]



J. Clin. Invest., 2013

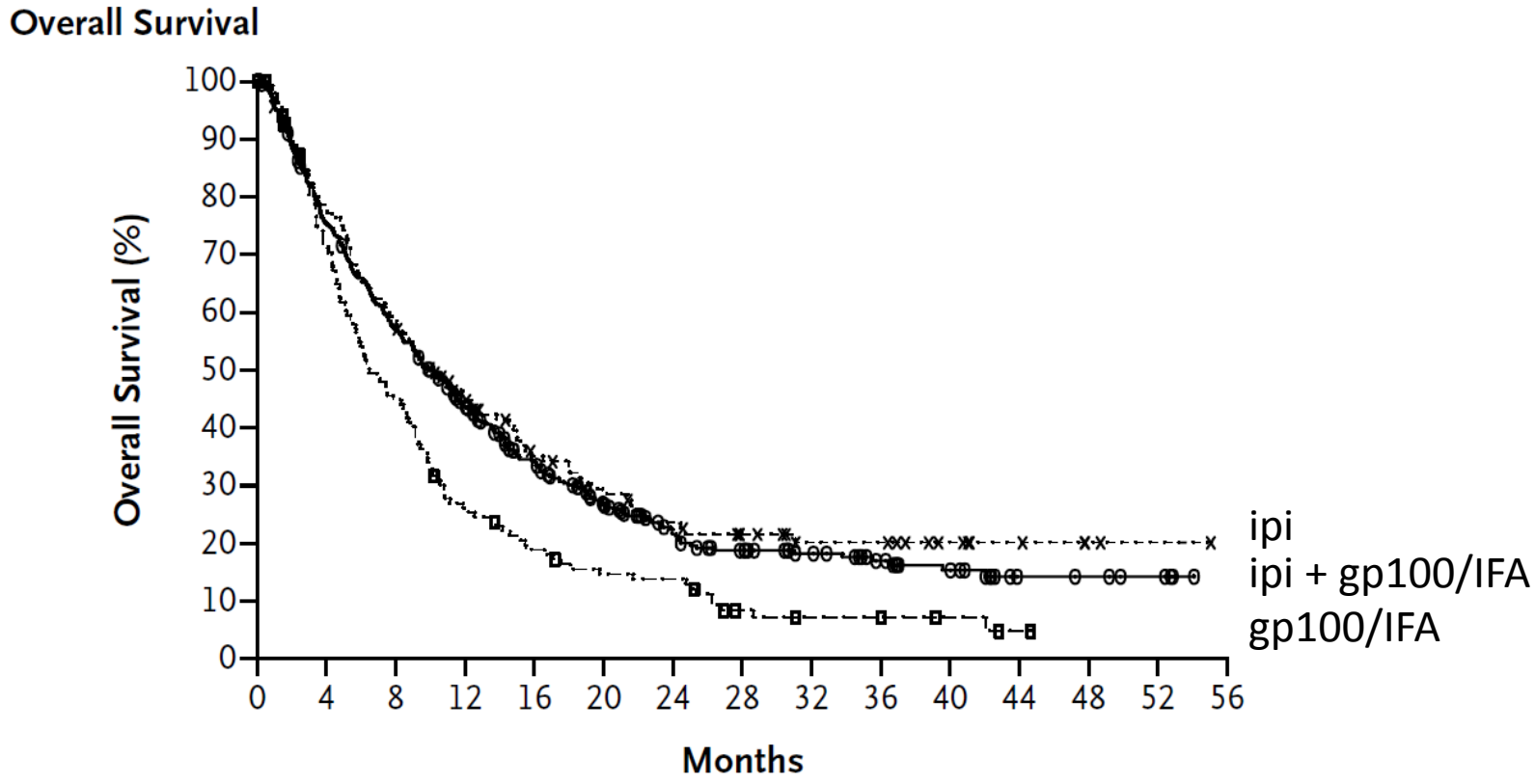
Checkpoint Blockade + Vaccines

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

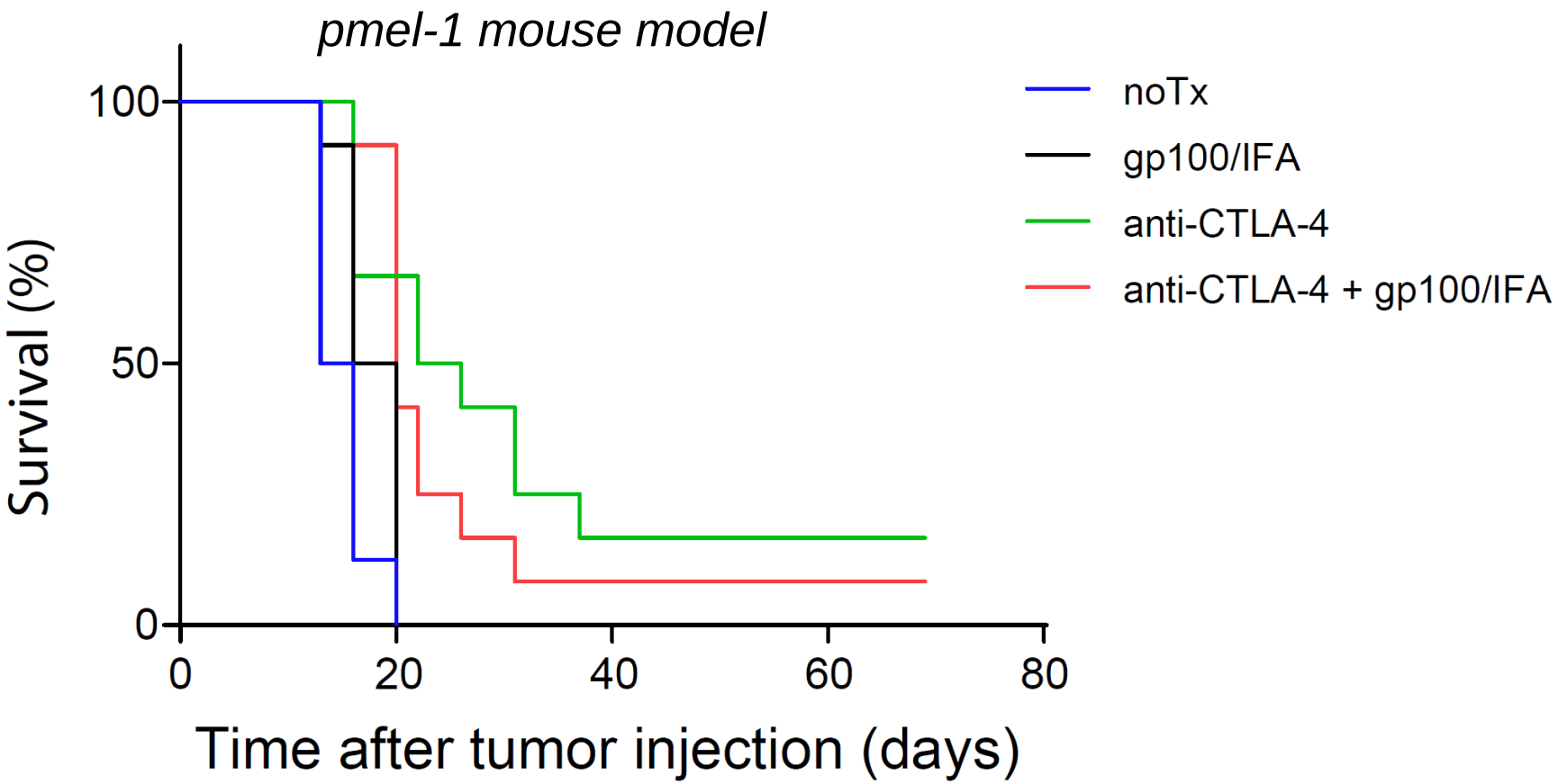
However, this was not observed.

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 Quirt, 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.

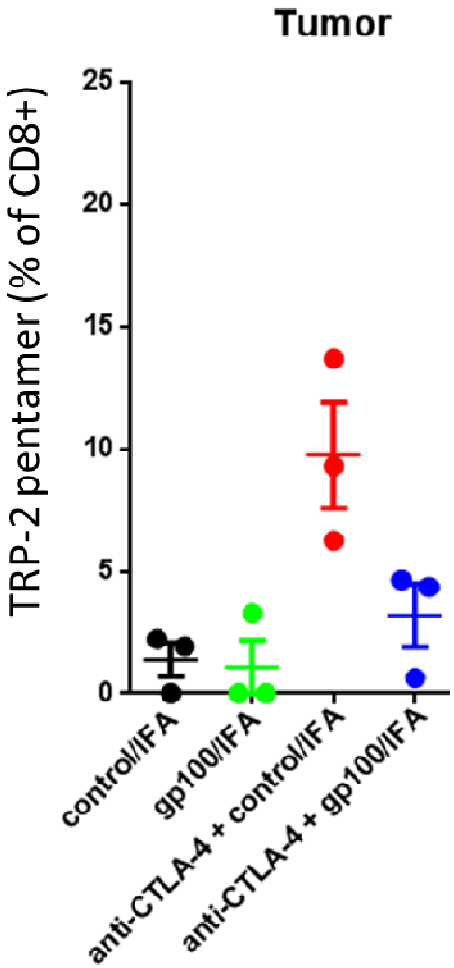


IFA-based vaccination does not synergize with anti-CTLA-4 therapy



Yared Hailemichael

IFA-based vaccination sequesters T cells induced by anti-CTLA-4 therapy



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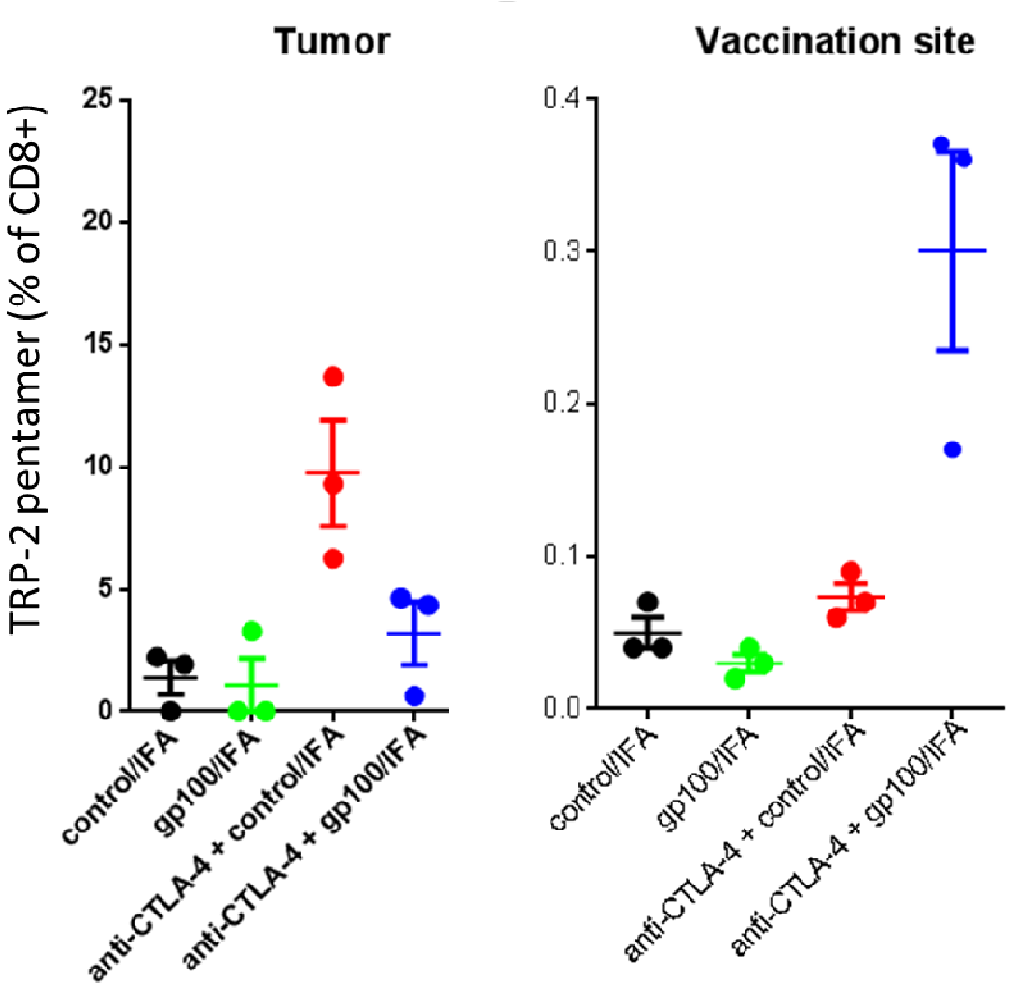
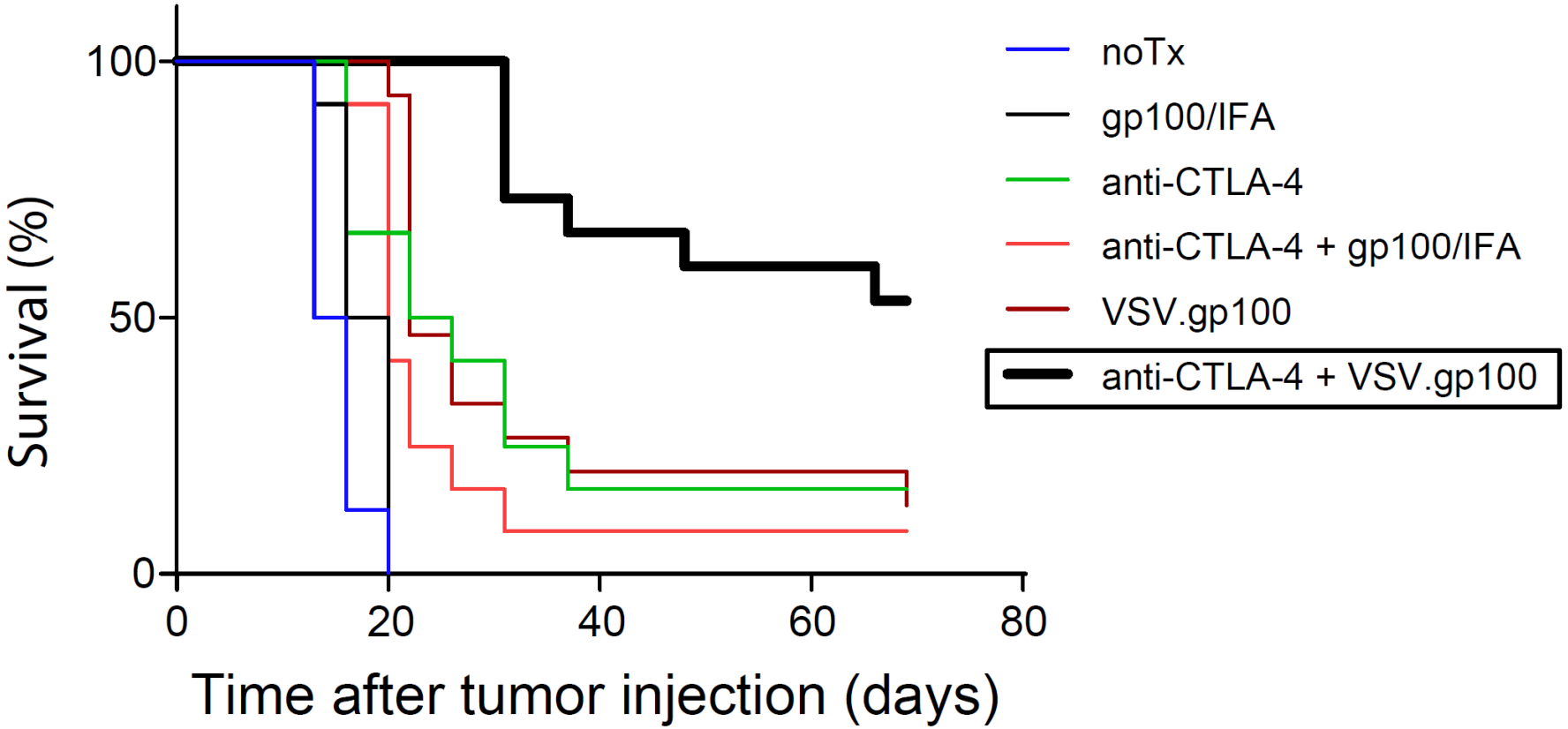
IFA-based vaccination sequesters T cells induced by anti-CTLA-4 therapy



Yared Hailemichael

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



Yared Hailemichael

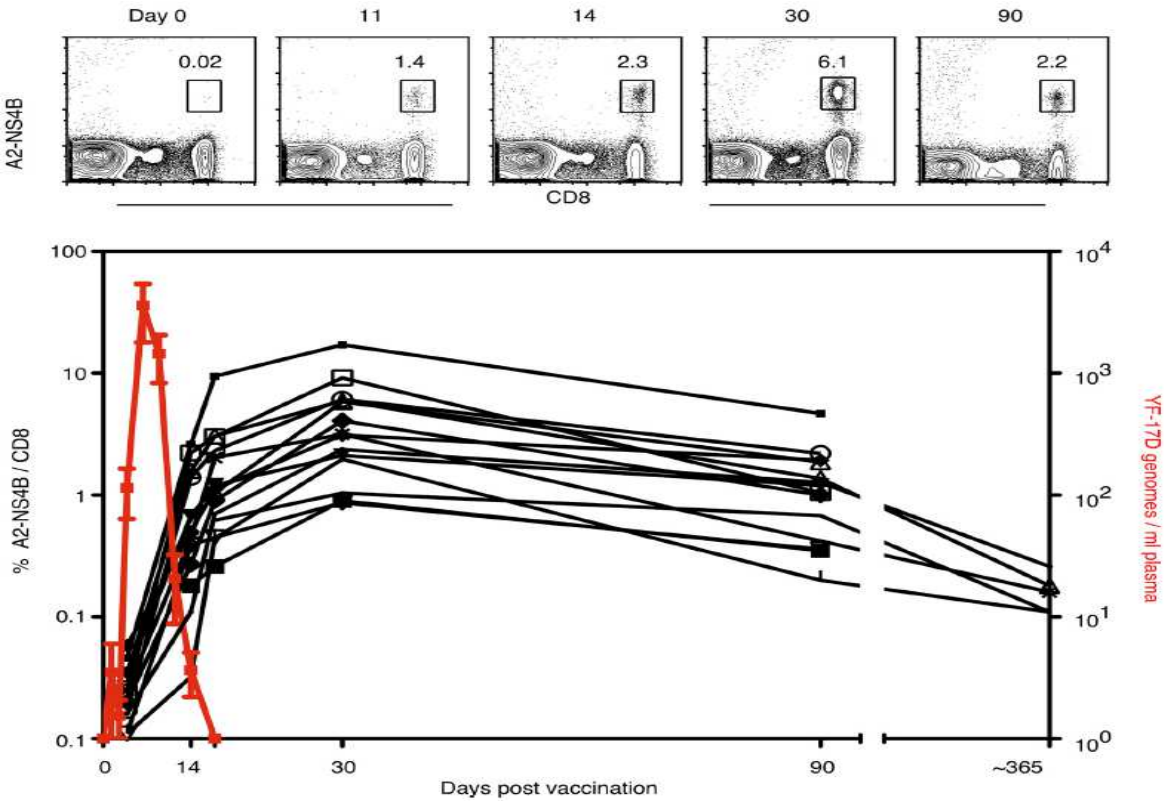
Current Cancer Vaccines Prime Few T cells:

Comparison with Anti-Viral T cells

The Yellow Fever Virus Vaccine Induces a Broad and Polyfunctional Human Memory CD8$^+$ T Cell Response[1]

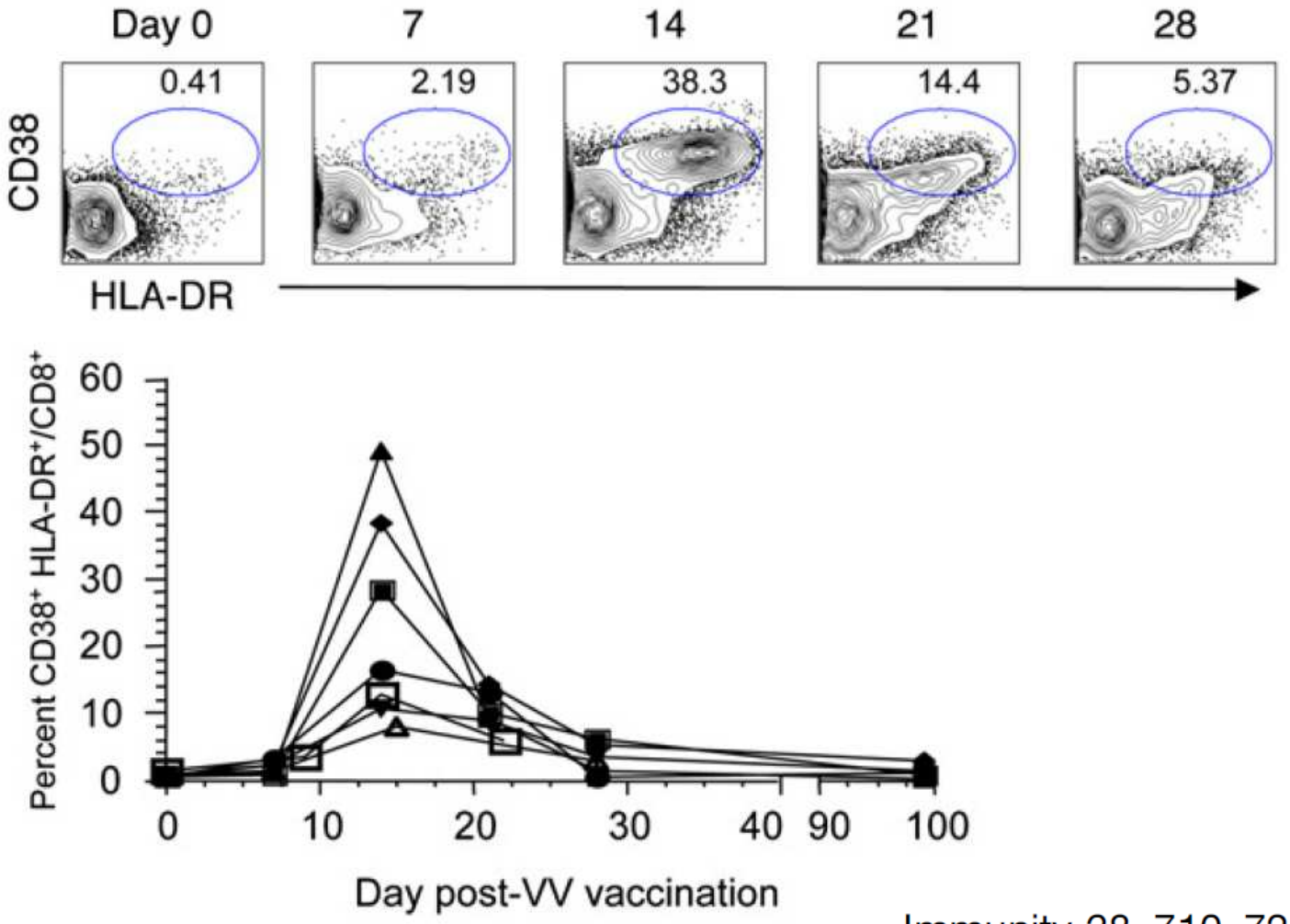
Rama S. Akondy,* Nathan D. Monson,* Joseph D. Miller,* Srilatha Edupuganti,* Dirk Teuwen,¶ Hong Wu,* Farah Quyyumi,* Seema Garg,* John D. Altman,* Carlos Del Rio,* Harry L. Keyserling,‡ Alexander Ploss,§ Charles M. Rice,§ Walter A. Orenstein,* Mark J. Mulligan,* and Rafi Ahmed[2]*†

The Journal of Immunology, 2009



Human Effector and Memory CD8$^+$ T Cell Responses to Smallpox and Yellow Fever Vaccines

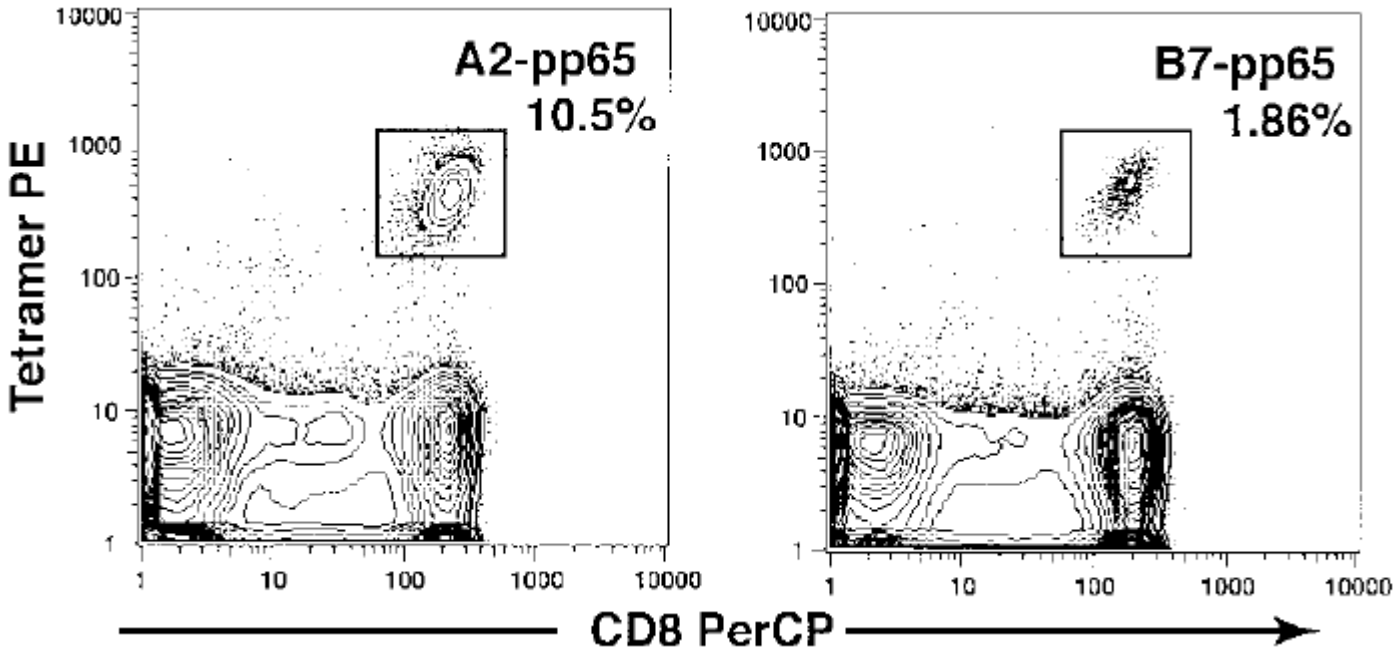
Joseph D. Miller,[1,2] Robbert G. van der Most,[1,2] Rama S. Akondy,[1] John T. Glidewell,[1] Sophia Albott,[1] David Masopust,[1] Kaja Murali-Krishna,[1] Patryce L. Mahar,[1] Srilatha Edupuganti,[1] Susan Lalor,[1] Stephanie Germon,[1] Carlos Del Rio,[1] Mark J. Mulligan,[1] Silvija I. Staprans,[1,3] John D. Altman,[1] Mark B. Feinberg,[1,3] and Rafi Ahmed[1,*]
[1]Emory Vaccine Center and the Hope Clinic, Emory University School of Medicine, Atlanta, GA 30322, USA



Immunity *28*, 710–722, May 2008

Cytomegalovirus reactivation following allogeneic stem cell transplantation is associated with the presence of dysfunctional antigen-specific $CD8^+$ T cells

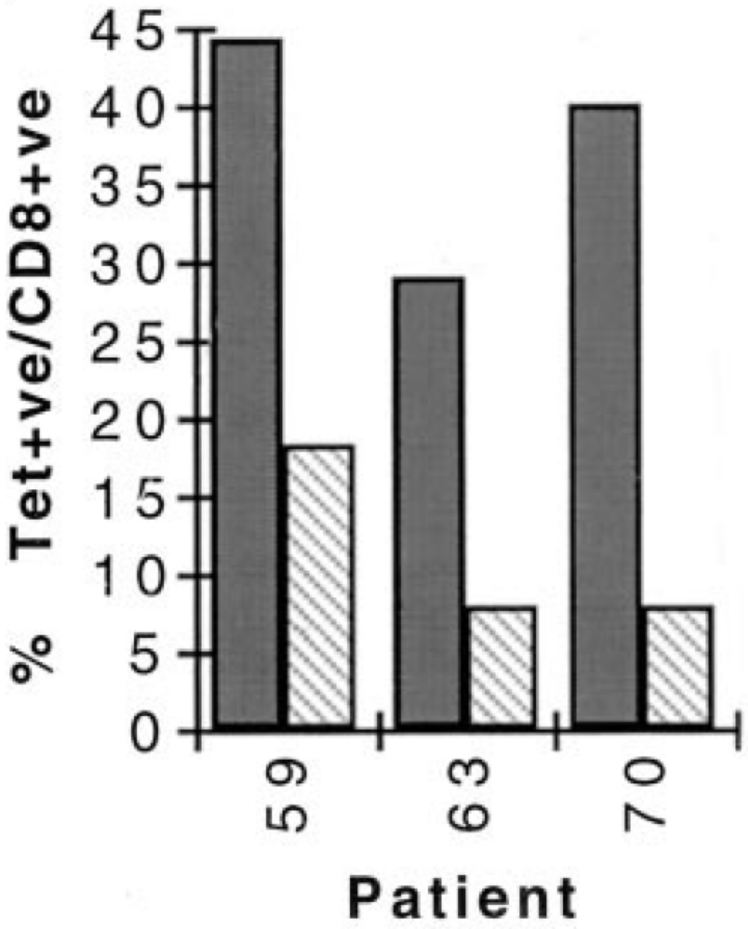
Evren Özdemir, Lisa S. St. John, Geraldine Gillespie, Sarah Rowland-Jones, Richard E. Champlin, Jeffrey J. Molldrem, and Krishna V. Komanduri



BLOOD, 15 NOVEMBER 2002

Direct Visualization of Antigen-specific CD8+ T Cells during the Primary Immune Response to Epstein-Barr Virus In Vivo

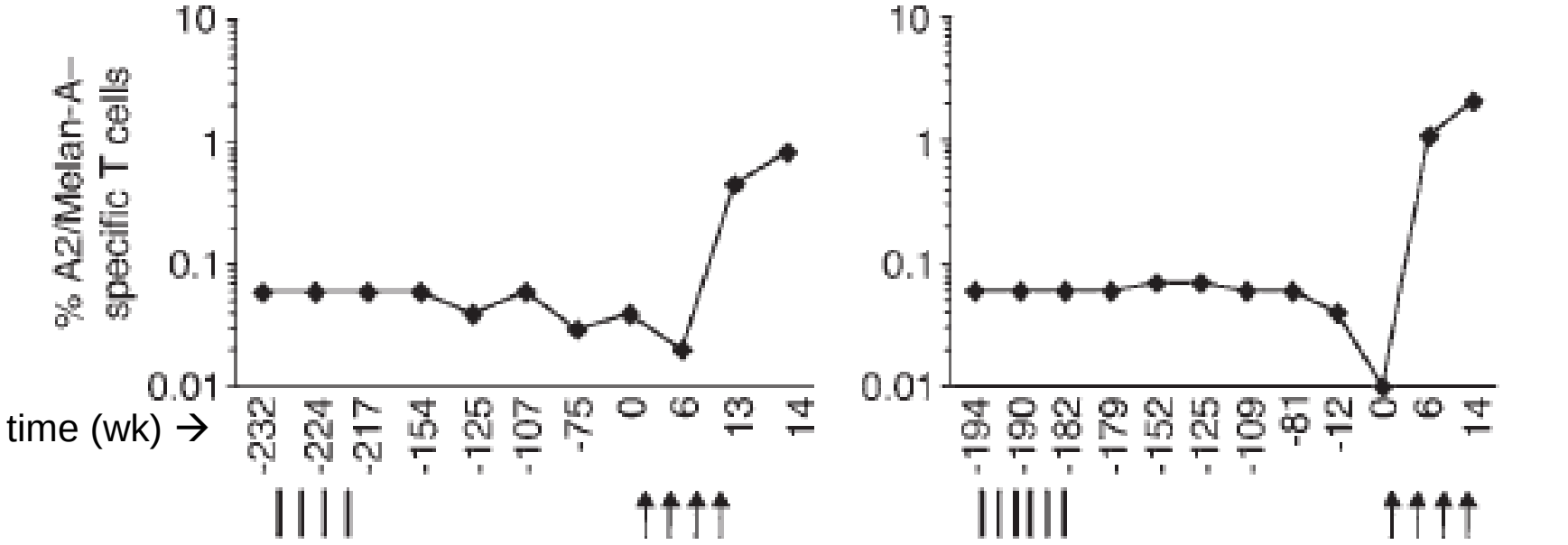
By M.F.C. Callan,* L. Tan,* N. Annels,‡ G.S. Ogg,* J.D.K. Wilson,* C.A. O'Callaghan,* N. Steven,‡ A.J. McMichael,* and A.B. Rickinson‡



J. Exp. Med. 187, 1998

Rapid and strong human CD8+ T cell responses to vaccination with peptide, IFA, and CpG oligodeoxynucleotide 7909

Daniel E. Speiser,[1] Danielle Liénard,[1,2] Nathalie Rufer,[3] Verena Rubio-Godoy,[1] Donata Rimoldi,[1] Ferdy Lejeune,[2] Arthur M. Krieg,[4] Jean-Charles Cerottini,[1,5] and Pedro Romero[1]



Vaccine Vaccine+CpG Vaccine Vaccine+CpG

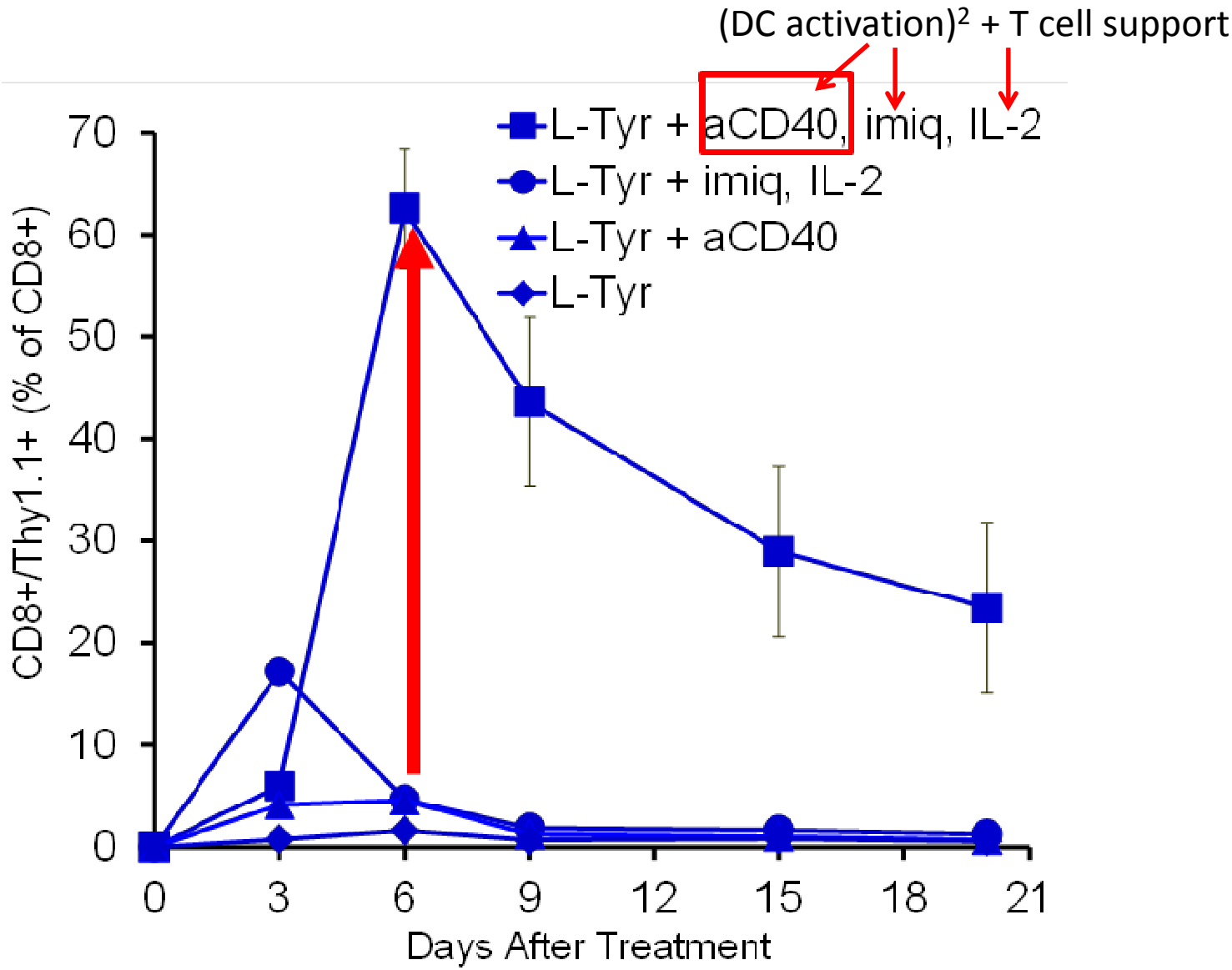
J. Clin. Invest. **115**:739–746 (2005)

Generalizing & Simplifying Conclusion

	anti-virus system	% of CD8+	# of epitopes
1.	mice - acute LCMV	>85	10
2.	mice - VSV.HIV-Env vaccine	40	1
3.	monkeys - SIV	5	1
4.	human - live Yellow Fever Vaccine	10	multiple
5.	human - live Vaccinia Vaccine	50	multiple
6.	human - CMV antigenemia	3	multiple
7.	human - acute EBV	35	1

	anti-tumor system	% of CD8+	epitopes
1.	human - canarypox	0, 0.1- 2	gp100-209.2M
2.	human - MVA-infected DCs	0.5	Tyrosinase-368
3.	human - UV-inactivated VV	0.01	gp100-209.2M
4.	human - peptide in IFA	0, 0.1-10	gp100-209.2M
5.	human - peptide in IFA	0, 0.1	gp100-209.2M,MART-1
6.	human - peptide in IFA	0, 0.1-3	gp100-209.2M

Combination Adjuvants are Key



Hiep Khong

Conclusions

- Peptide vaccines can have clinical impact
- T cell responses tend to be (too) low
- Formulation matters: possible T cell sequestration
- Use mutated peptides?

- **To induce better T cell / clinical responses:**
- Use multiple peptides
- Select strong MHC binders
- Use long peptides – probably
- Add immunomodulators (cytokines, TLR agonists)
- Add GM-CSF – likely vaccine-dependent
- Add CD4 helper peptides – not clear
- Induce CD40 triggering – definitely
- Combine with checkpoint blockade
- Combination Vaccines: Multiple Immunostimulatory Molecules