Society for Immunotherapy of Cancer (SITC)

Oncolytic Viruses and Their Application to Cancer Immunotherapy

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Josephine Ford Cancer Institute

Advances in Cancer Immunotherapy™ - Michigan
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Presentation originally prepared and presented by

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MD Anderson Cancer Center
Houston, TX, USA

Society for Immunotherapy of Cancer

Disclosures

- None for SITC presentation
- Phase I Clinical Trials supported by:

  Abbvie, AstraZeneca/MedImmune, EMD-Serono, Celgene, GSK, ImClone/Lilly, Millennium/Takeda, Novartis, Regeneron, TEVA, etc.
- NCI/Intergroups: NSABP/RTOG/GOG (NRG), SWOG

Overview

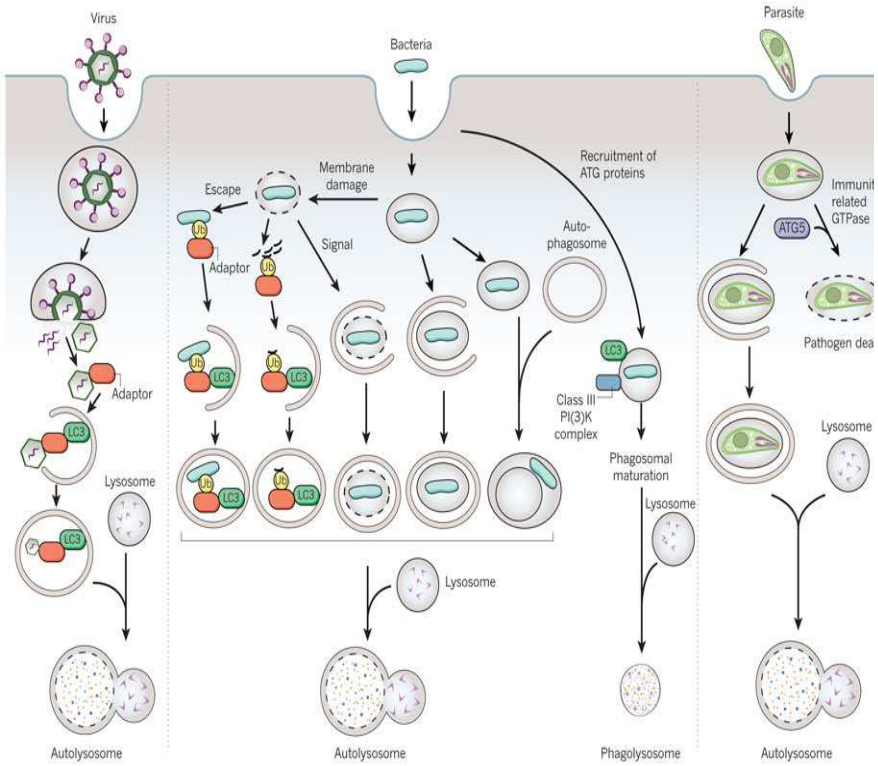
- What are oncolytic viruses (OV)
- Why use oncolytic viruses in cancer therapy
- What is a Cancer Vaccine
- Genetic basis for cancer vaccine and anti-cancer immunity
- Oncolytic viruses-mediated cancer immunotherapies
- Research and clinical development of immunotherapies in cancer

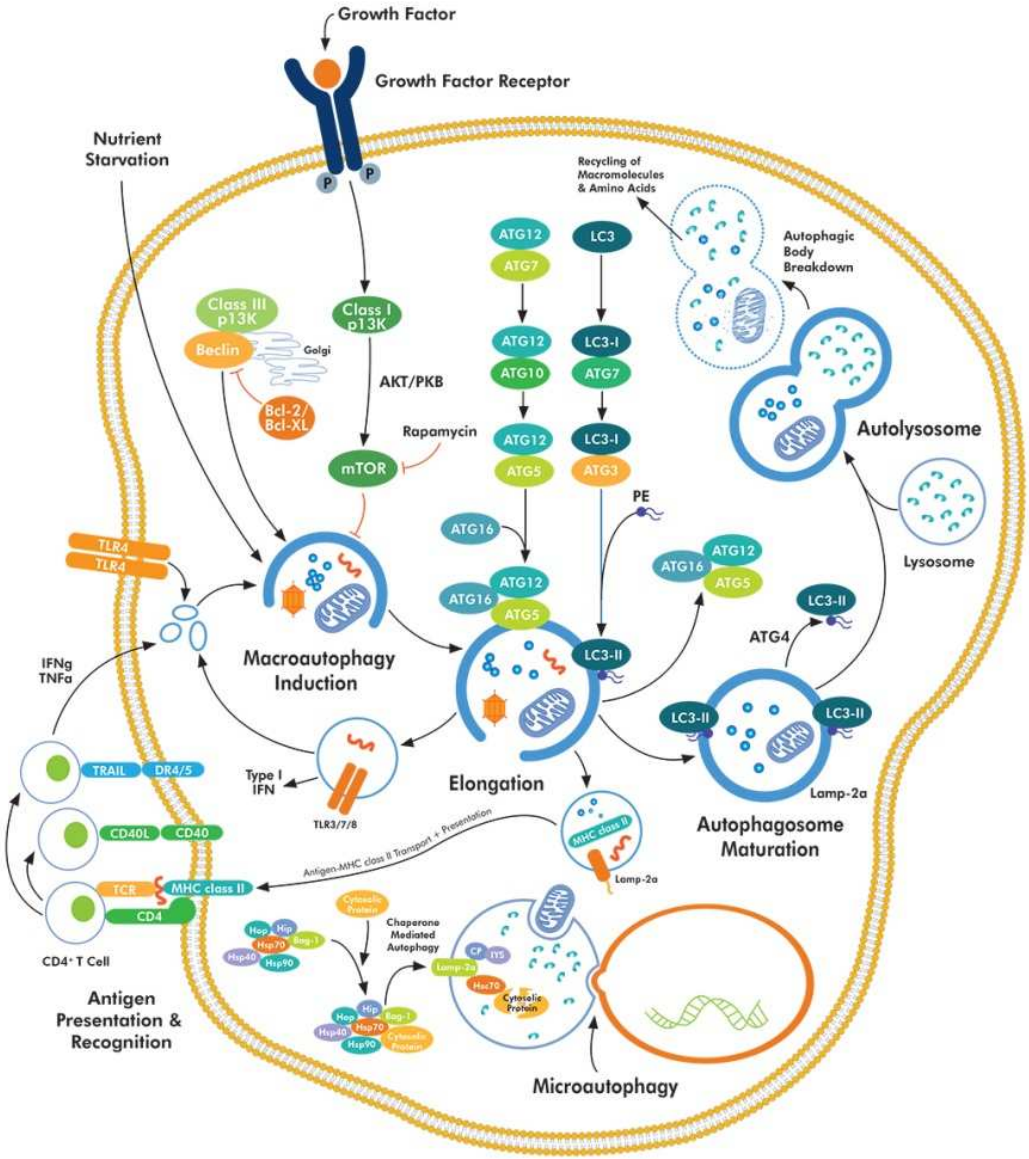
What Are Oncolytic Viruses

- **Oncolytic viruses (OVs)**
  - Preferentially select cancer cells (viral tropism) as their cellular replication hosts
  - Kill infected cancer and endothelial cells via direct oncolysis
  - Indirectly kill uninfected cells
    - Tumor vasculature targeting
    - By stander effect

- **Mechanism of actions of OVs via multimodal immunogenic cell death (ICD)**
  - Autophagy
  - Efficient cross-present TAA
  - Adaptive anticancer immunity
  - Genetic engineered
    - GM-CSF (T-VEC & Pexa-Vec)
    - Toll-like receptor (TLR)

Autophagy





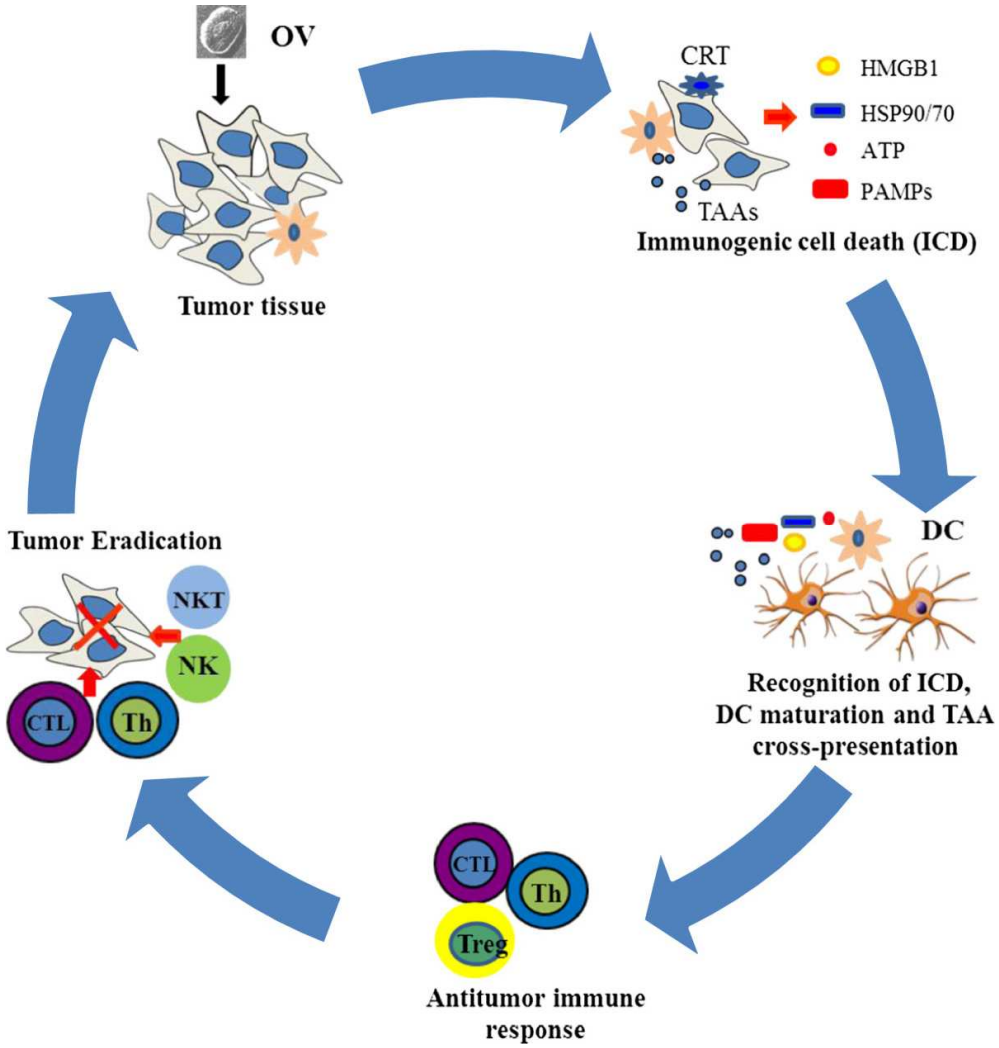
http://www.nature.com/nature/journal

What Are Oncolytic Viruses

- Non-pathogenic in humans and viruses naturally replicate in cancer cells
  - Autonomous parvoviruses
  - Myxoma virus (poxvirus)
  - Newcastle disease virus (Paramyxovirus)
  - Reovirus
  - Seneca valley virus
- Viruses can be genetically manipulated as vaccine vectors
  - Measles virus
  - *Poliovirus (picornavirus)*
  - Vaccinia virus (poxvirus)
  - Adenovirus
  - Herpes simplex virus
  - Vesicular stomatitis virus (rhabdovirus)

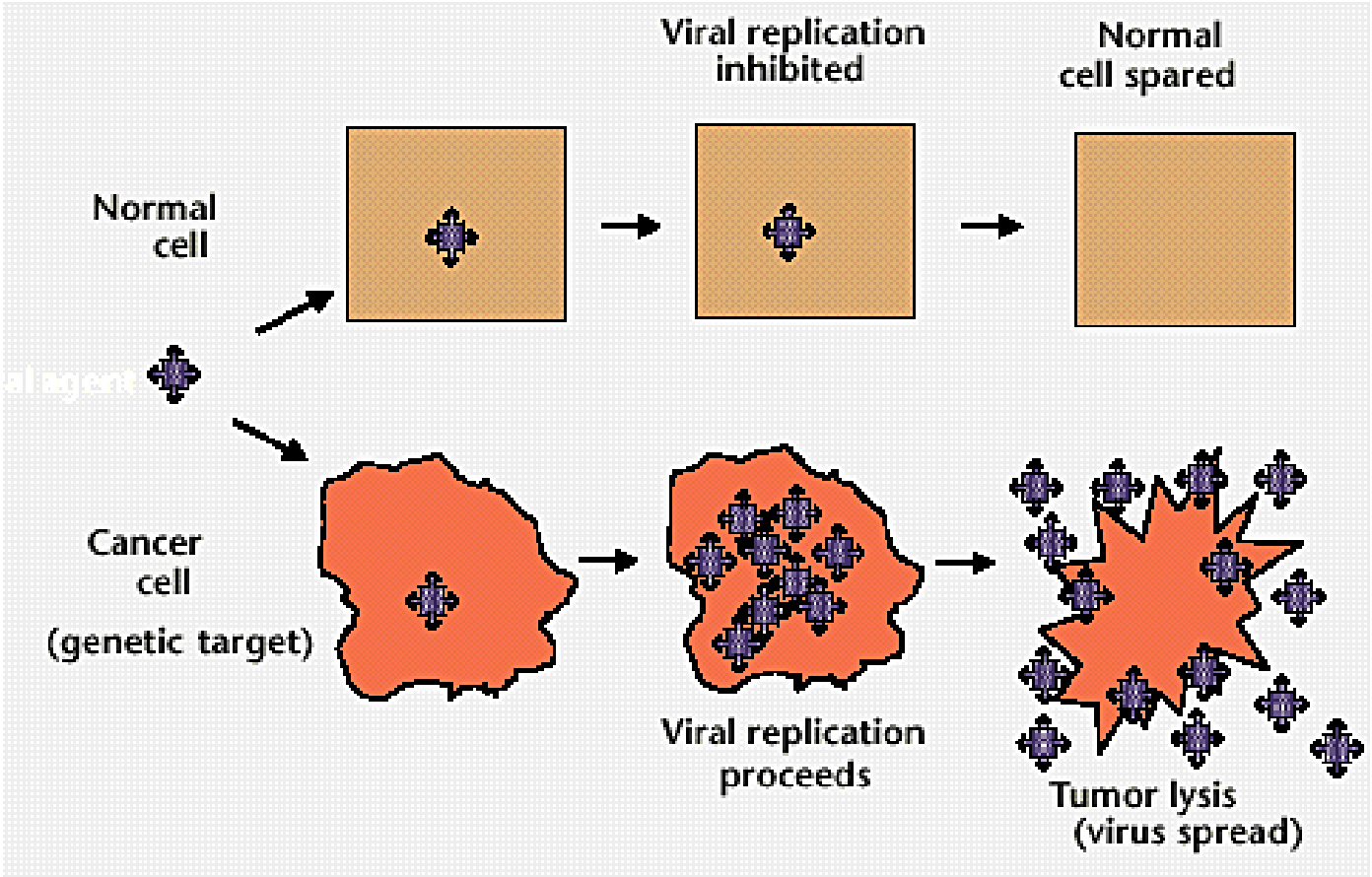
Why Use Oncolytic Viruses

- Oncolytic viruses can selectively (*Tropism*) infect and damage cancerous tissues without causing harm to normal tissues
- *Tropism*: the ability of a virus to recognize cell surface features that mediate viral genome entry into the host cell
- Each virus has a specific cellular tropism that determines which tissues are preferentially infected
  - Rabies and polio to neurons
  - Hepatitis A/B/C viruses
  - HIV toward T-helper cells



Bartlett *et al. Molecular Cancer* 2013 **12**:103 doi:10.1186/1476-4598-12-103

Schematic representation of tumor-selective viral replication and oncolysis



*David Kirn, et al. Nature Medicine **7**, 781 - 787 (2001)*

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What is a Cancer Vaccine?

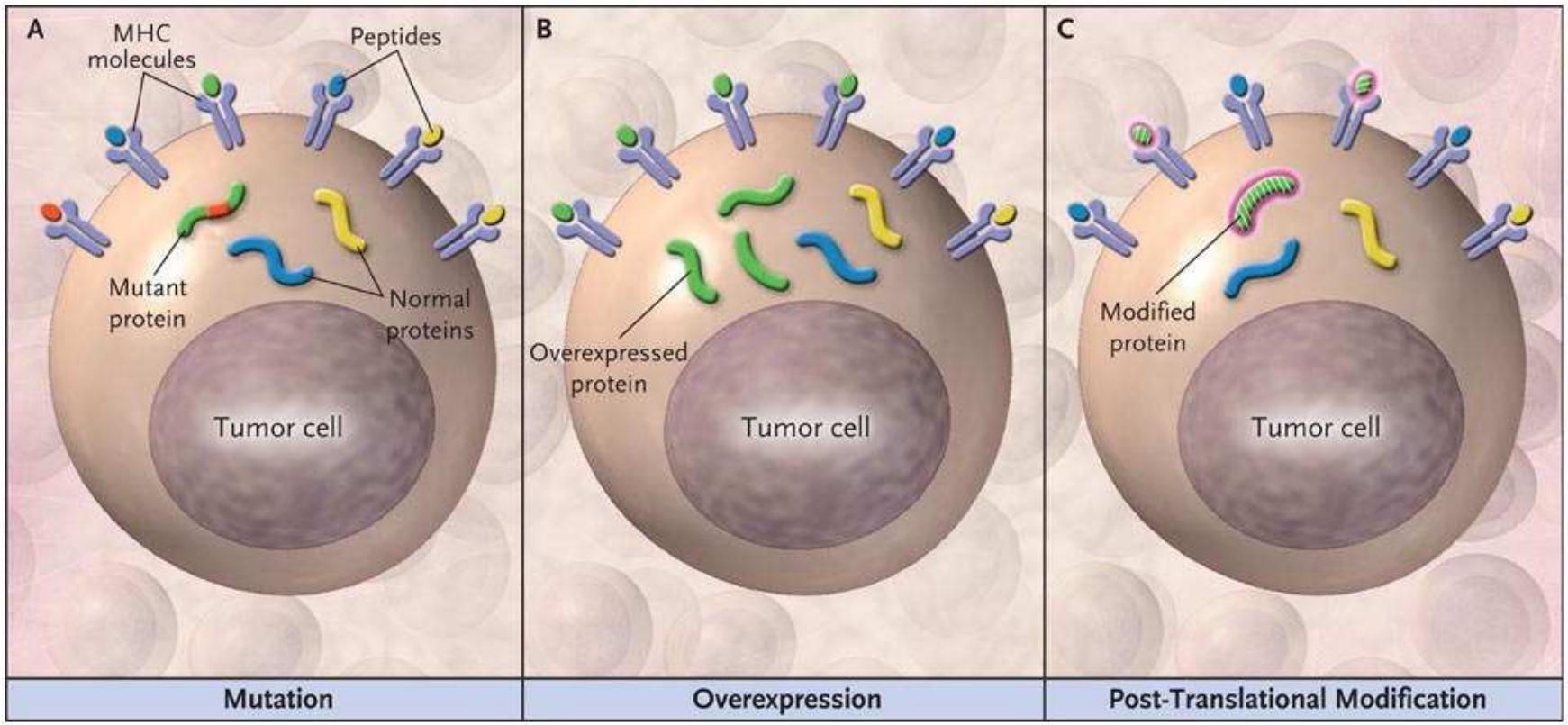
peptide(s)

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

Result: specific anti-tumor immunity

What are Tumor-Associated Antigens?

Three Ways for Self Antigens to Become Tumor Antigens

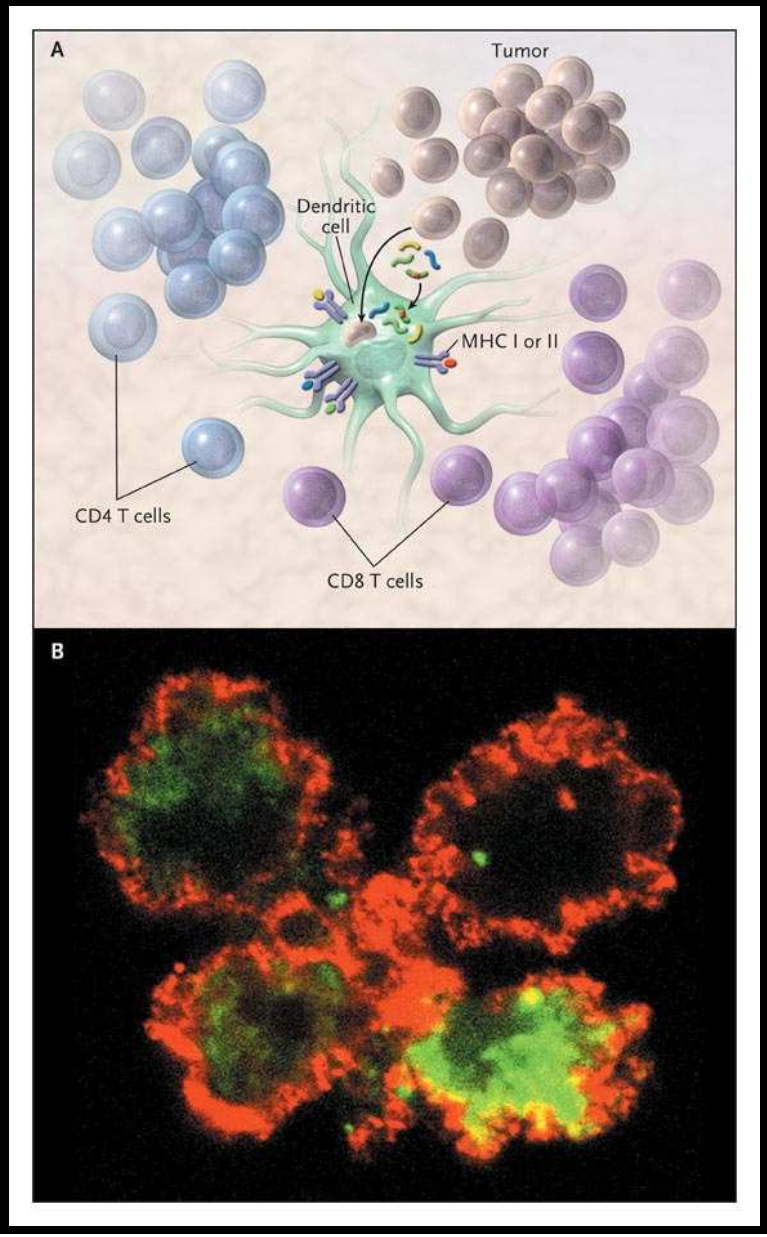


?Relationship between TAA expression and histologic differentiation?

Finn OJ. N Engl J Med 2008;358:2704-2715.

The NEW ENGLAND JOURNAL of MEDICINE

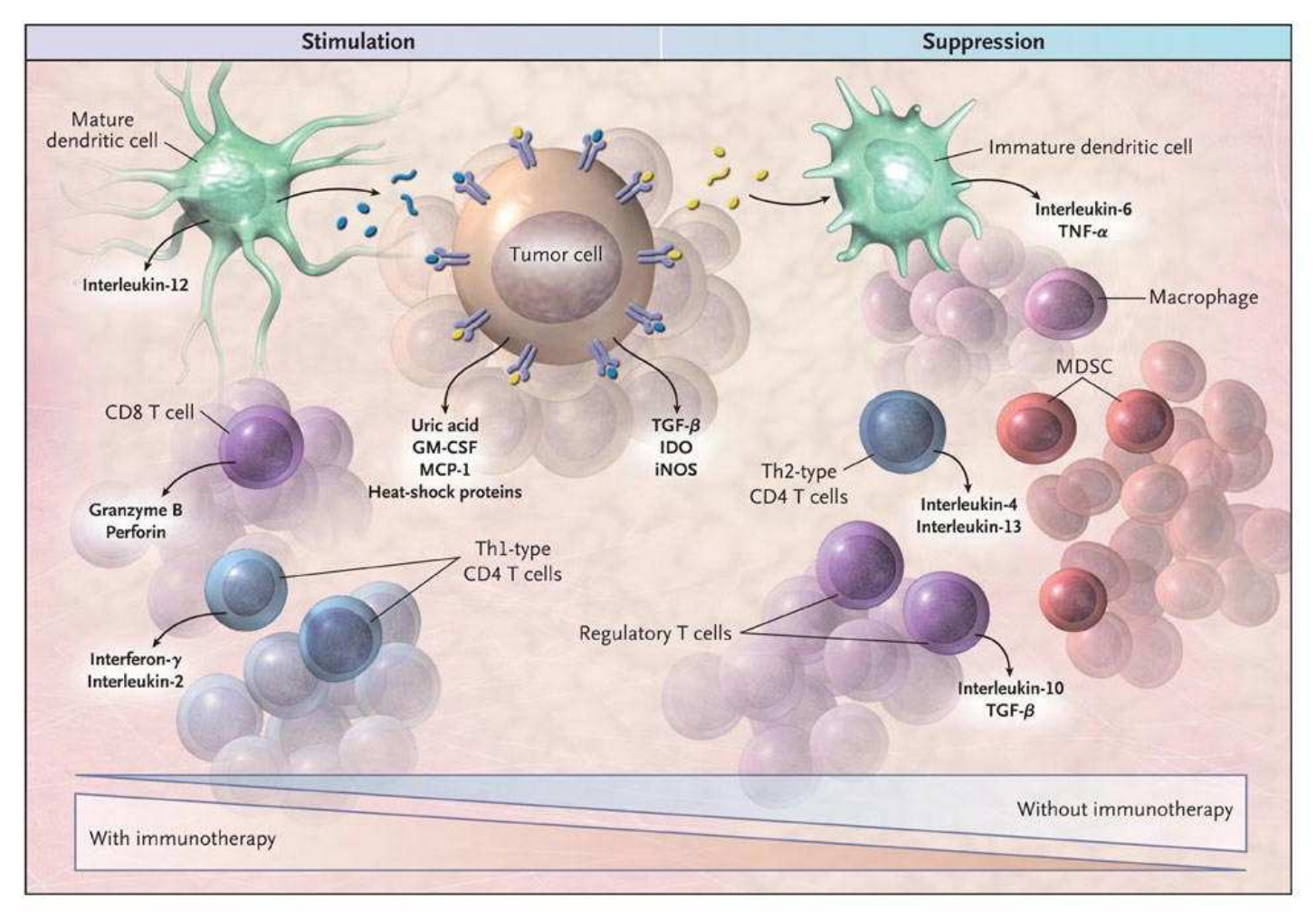
Tumor Antigens Eliciting T-Cell Immunity When Presented to Naive T Cells by Antigen-Presenting Dendritic Cells.



Finn OJ. N Engl J Med 2008;358:2704-2715.

The NEW ENGLAND JOURNAL of MEDICINE

Immunostimulatory and Immunosuppressive Forces in the Tumor Microenvironment.

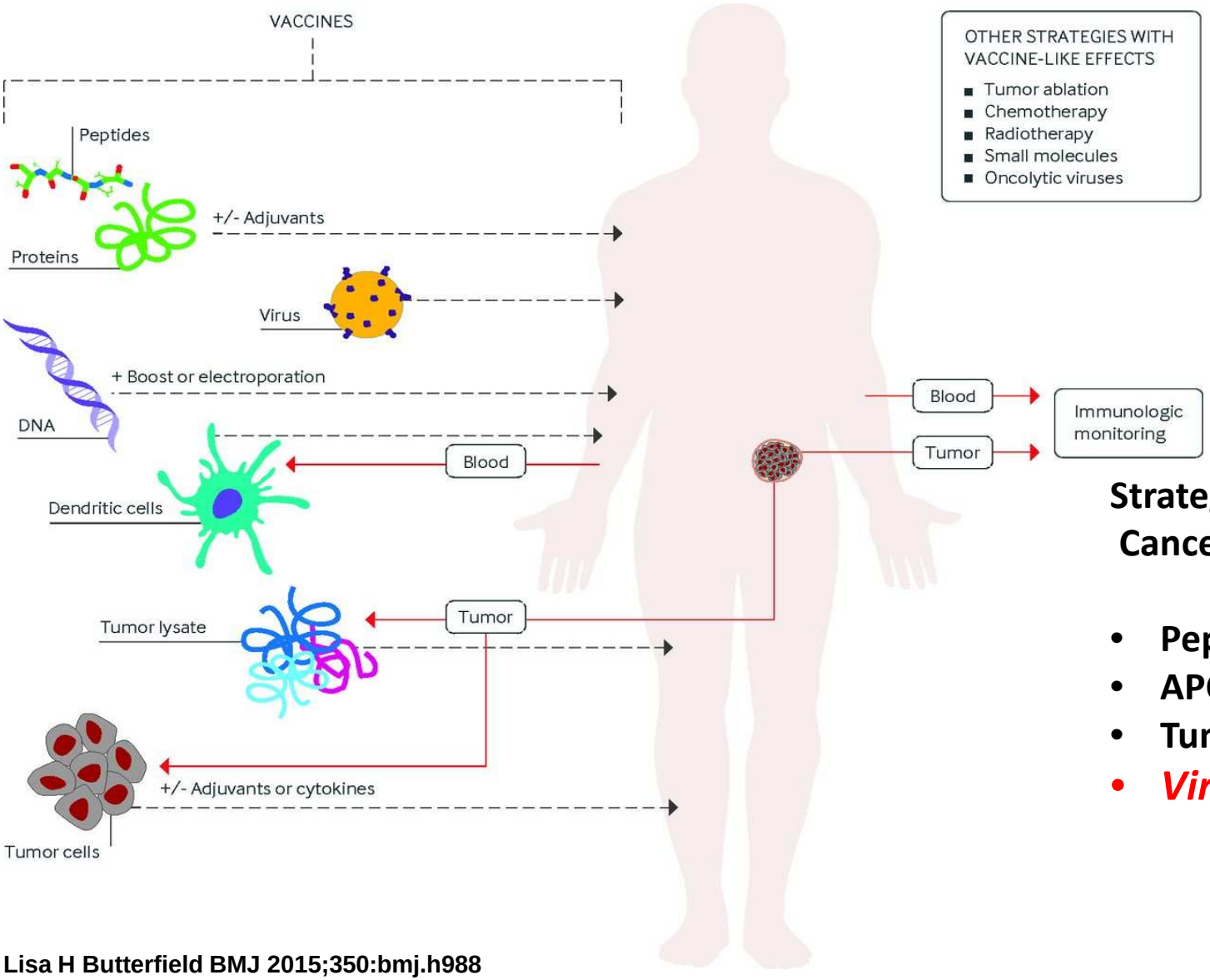


The balance between the immunostimulation and immunosuppression

Finn OJ. N Engl J Med 2008;358:2704-2715.

The NEW ENGLAND JOURNAL of MEDICINE

What is a Cancer Vaccine?



Strategies & Types of Cancer Vaccines

- **Peptide-based**
- **APC-based**
- **Tumor-based**
- ***Virus-based***

Lisa H Butterfield BMJ 2015;350:bmj.h988

thebmj

When could cancer vaccines be useful?

- **Cancer Prevention**
  - **HPV vaccine, HBV vaccine, etc.**
- **Cancer therapy**

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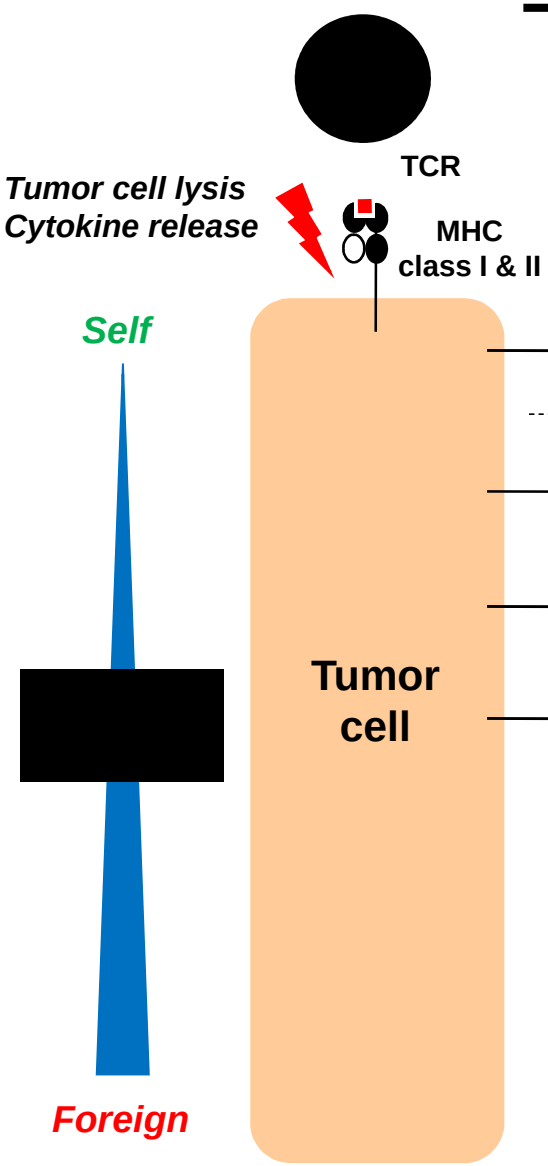
Tumor-Associated Antigens



Non-mutated antigens (normal or self-antigens)

→ **Self Ags - ubiquitous, not tumor-specific (eg. actin, vimentin) > *98%***

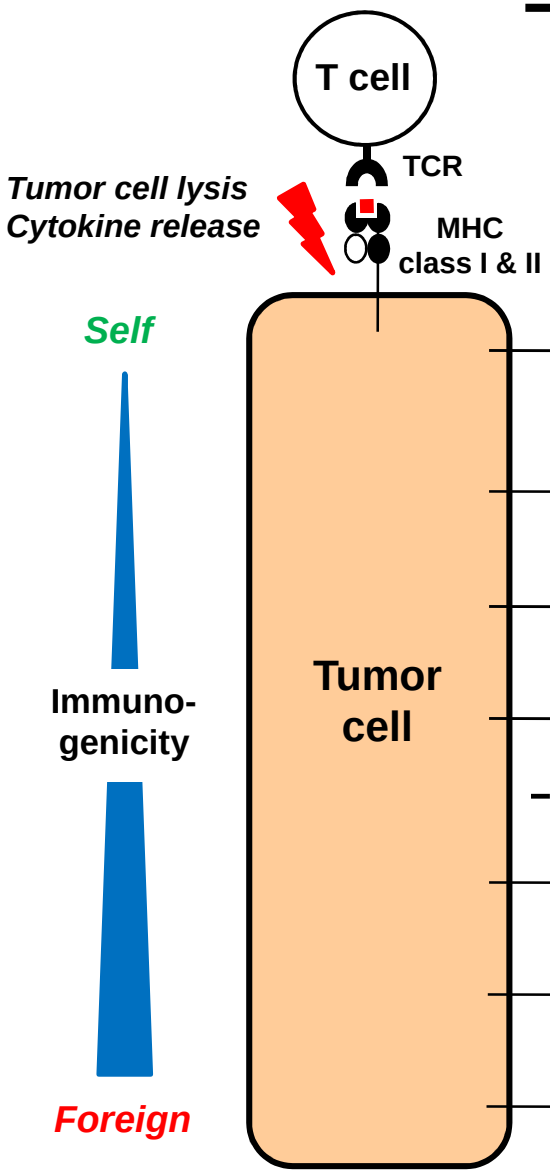
→ **Tissue differentiation Ags (eg. gp100, Tyrosinase, MART-1/Melan-A)**

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

→ **Single point mutations**

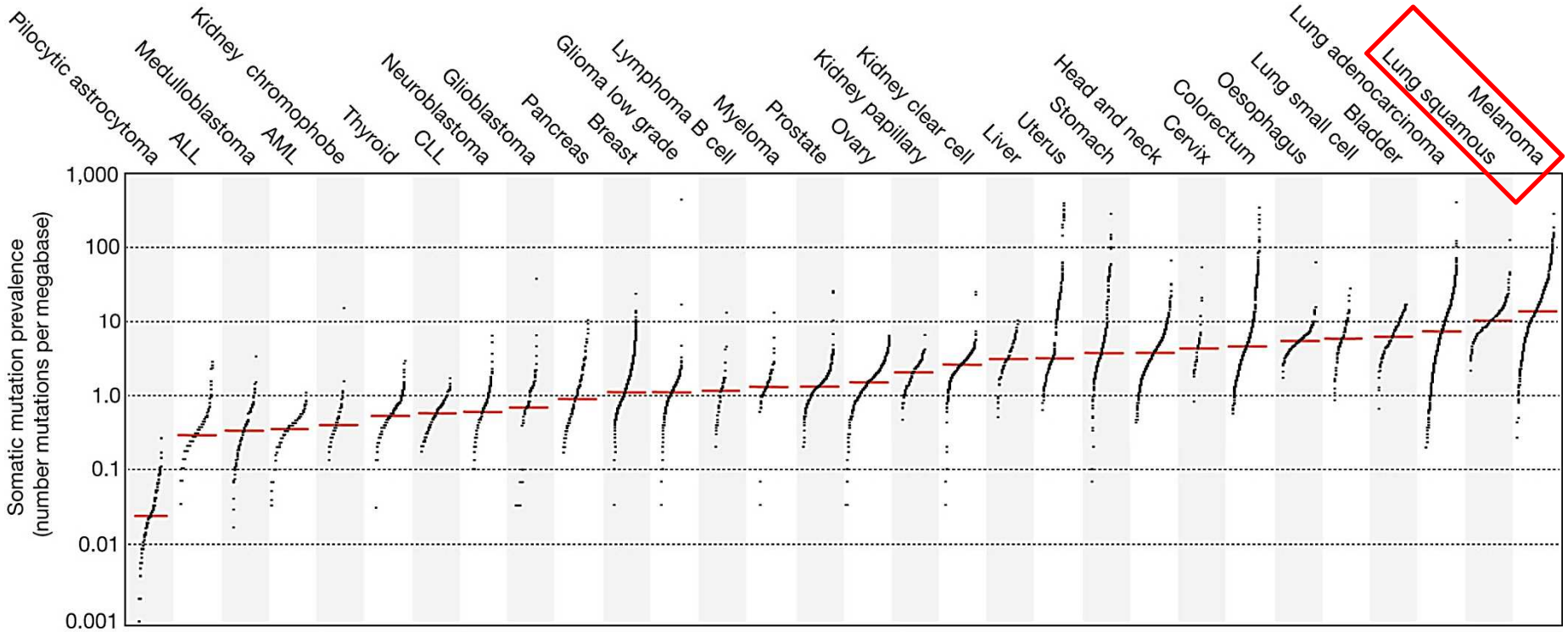
→ **Deletions / insertions / frameshifts**

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

Mutated antigens (aberrant), therefore, tumor-specific

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

The prevalence of somatic mutations across human cancer types



LB Alexandrov *et al. Nature* **500(7463):** 415-421 (2013) doi:10.1038/nature12477

nature

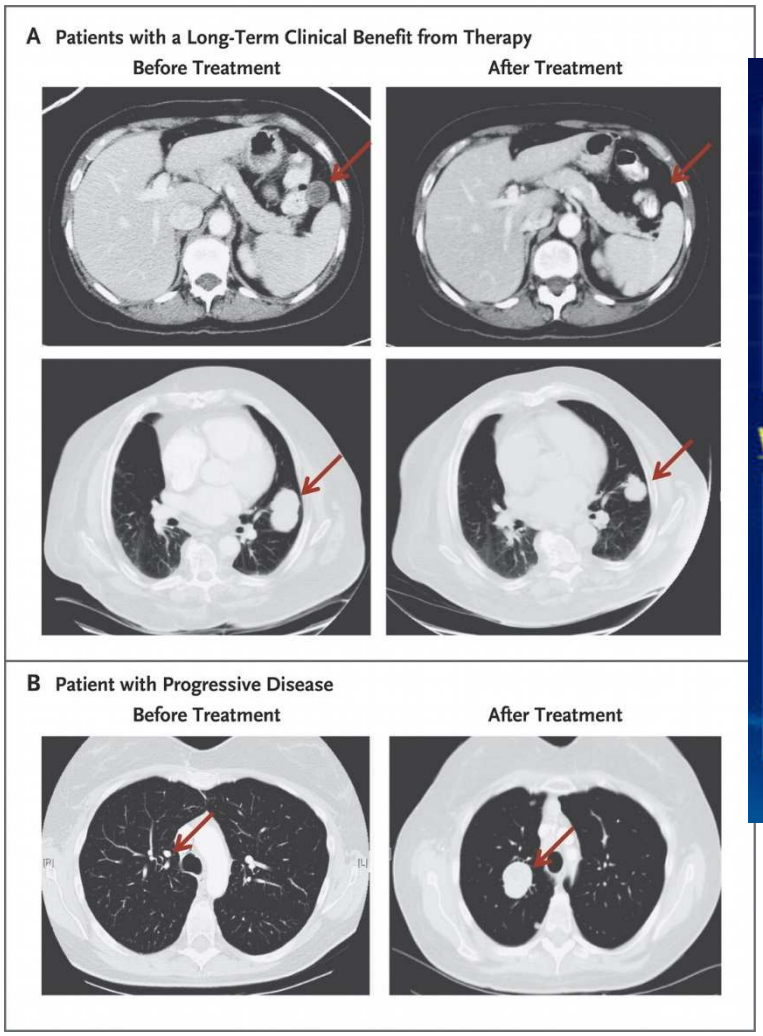
The NEW ENGLAND JOURNAL of MEDICINE

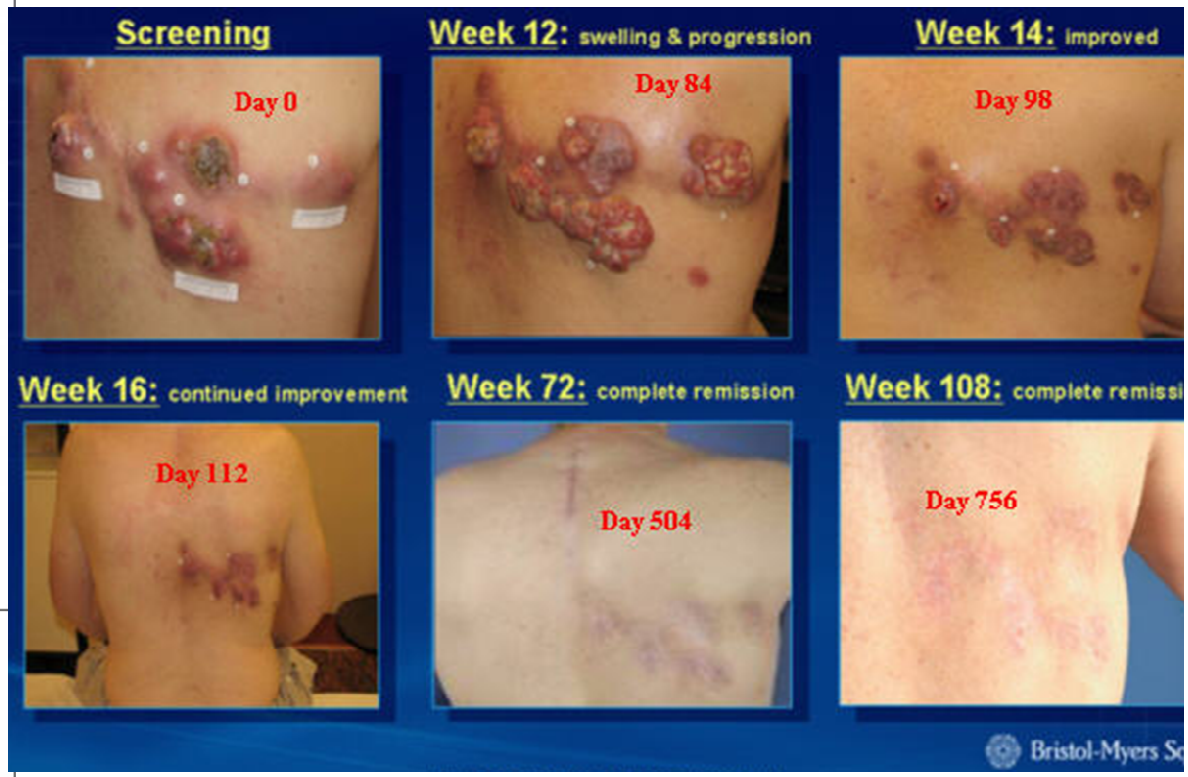
ORIGINAL ARTICLE

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.

Snyder A et al. N Engl J Med 2014;371:2189-2199.

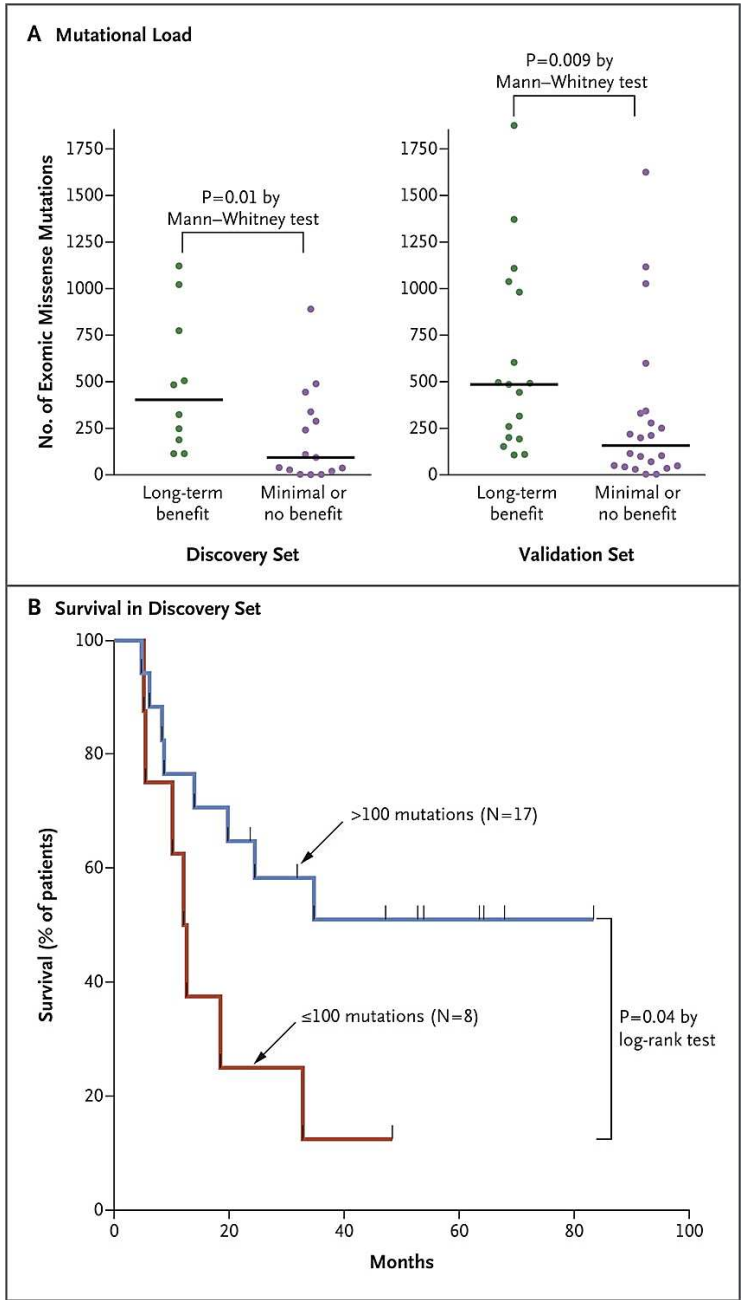




Clinical response to anti-CTLA4 (Ipilumab) in a patient with cutaneous melanoma (BMS Data)

Snyder A et al. N Engl J Med 2014;371:2189-2199.

Mechanism of Actions: Neo-Antigens and Anti-Clinical Response



- **Neoantigens landscape present in** melanoma
- TCR cross-reactivity and positive selection in the thymus and sculpting by evolution in TCR
- HLA genes may have helped to mold the motifs
- T-cell–recognition motifs present in T cells that underlie immunotherapy response
- Previously exposed to organisms with antigens homologous to tumor neoantigens and may have undergone priming

Snyder A et al. N Engl J Med 2014;371:2189-2199.

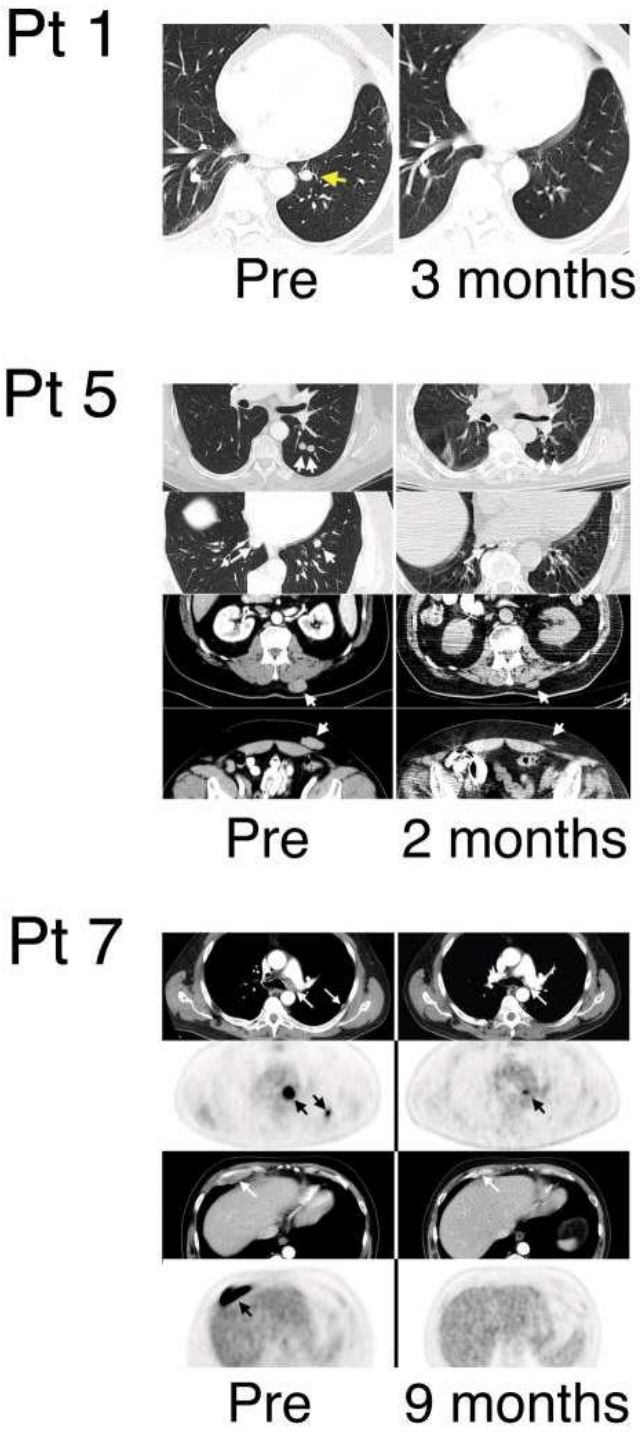
Clinical Trials of Cancer Vaccines

415 open studies using cancer vaccines on 30JUL2015 (www.clinicaltrial.gov)

altrials.gov/ct2/results?term=cancer+vaccine&recr=Open — CT Search of: cancer vaccine | ...

Tools Help

2	Recruiting	Safety & Efficacy Study of EGF Cancer Vaccine to Treat Stage IV Biomarker Positive, Wild Type EGF-R NSCLC Patients	**Condition:** Carcinoma, Non-Small-Cell Lung **Intervention:** Biological: EGF Vaccine
3	Recruiting	A Phase I Study With a Personalized NeoAntigen Cancer Vaccine in Melanoma	**Condition:** Melanoma **Interventions:** Biological: Poly-ICLC; Biological: Peptides
4	Not yet recruiting	An Individualized Anti-Cancer Vaccine in Advanced Hepatocellular Carcinoma Subjects	**Condition:** Advanced Adult Hepatocellular Carcinoma **Interventions:** Biological: AlloVax; Biological: AlloStim; Biological: CRCL
5	Recruiting	Safety Study of a Dendritic Cell-based Cancer Vaccine in Melanoma	**Conditions:** Melanoma; Tumor Vaccines; Effects of Immunotherapy **Intervention:** Biological: GeniusVac-Mel4
6	Recruiting	Ph I Personalized NeoAntigen Cancer Vaccine With Radiotherapy for Patients With MGMT Unmethylated, Newly Diagnosed Glioblastoma	**Conditions:** Glioblastoma; MGMT-unmethylated Glioblastoma; Gliosarcoma; Glioblastoma With Oligodendroglial Features; Giant Cell Glioblastoma; Glioblastoma Multiforme **Interventions:** Radiation: Radiation Therapy; Biological: Personalized NeoAntigen Vaccine
7	Not yet recruiting	Safety and Immunogenicity of a Personalized Synthetic Long Peptide Breast Cancer Vaccine Strategy in Patients With Persistent Triple-Negative Breast Cancer Following Neoadjuvant Chemotherapy	**Conditions:** Triple Negative Breast Cancer; Triple Negative Breast Neoplasms; Triple-Negative Breast Cancer **Interventions:** Biological: Personalized synthetic long peptide vaccine (Poly ICLC); Drug: Poly ICLC
8	Not yet recruiting	Immunotherapy of Metastatic Colorectal Cancer	**Condition:** Colorectal Cancer Metastatic **Interventions:** Biological: AlloStim; Procedure: Cryoablation
9	Not yet recruiting	Neoadjuvant/Adjuvant GVAX Pancreas Vaccine (With CY) With or Without Nivolumab Trial for Surgically Resectable Pancreatic Cancer	**Condition:** Pancreatic Cancer **Interventions:** Drug: Cyclophosphamide; Biological: GVAX pancreatic cancer; Drug: Nivolumab
10	Recruiting	To Identify HLA-A1101-restricted Peptide Epitopes Derived From Novel Oncoantigens (URLC10, KIF20A, and CDCA1) Applicable for Cancer Vaccine in Singapore	

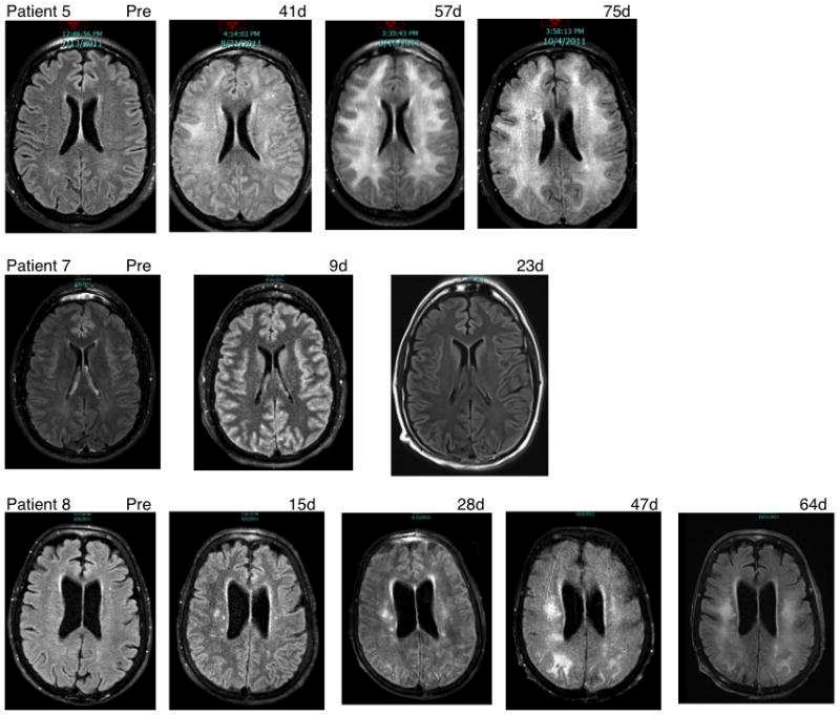


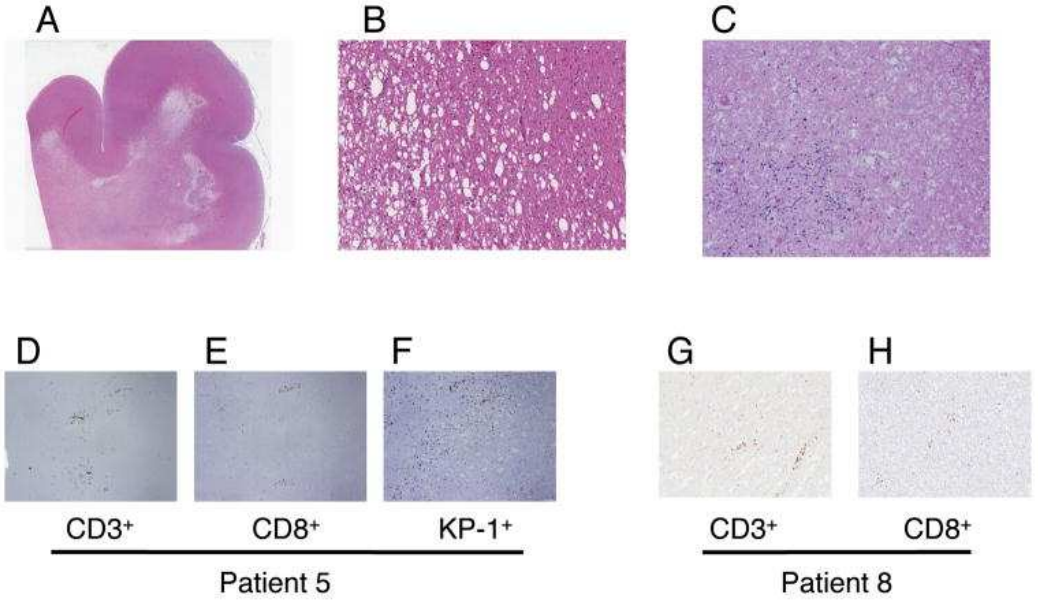
Clinical Anti-Cancer Responses

- MAGE-A3 is a tumor-specific protein
  - melanoma, non-small cell lung cancer, hematologic malignancies
- Expression of MAGE-A3 in lung adenocarcinoma were associated with shorter survival
- Targeting MAGE-A3:
  - A fusion protein of MAGE-A3 and *Haemophilus influenzae* protein D, combined with a proprietary immunoadjuvant

Robert A. Morgan, et al. J Immunother. 2013 February ; 36(2): 133–151.

MAGE-A3 TCR Related Neurologic Toxicity

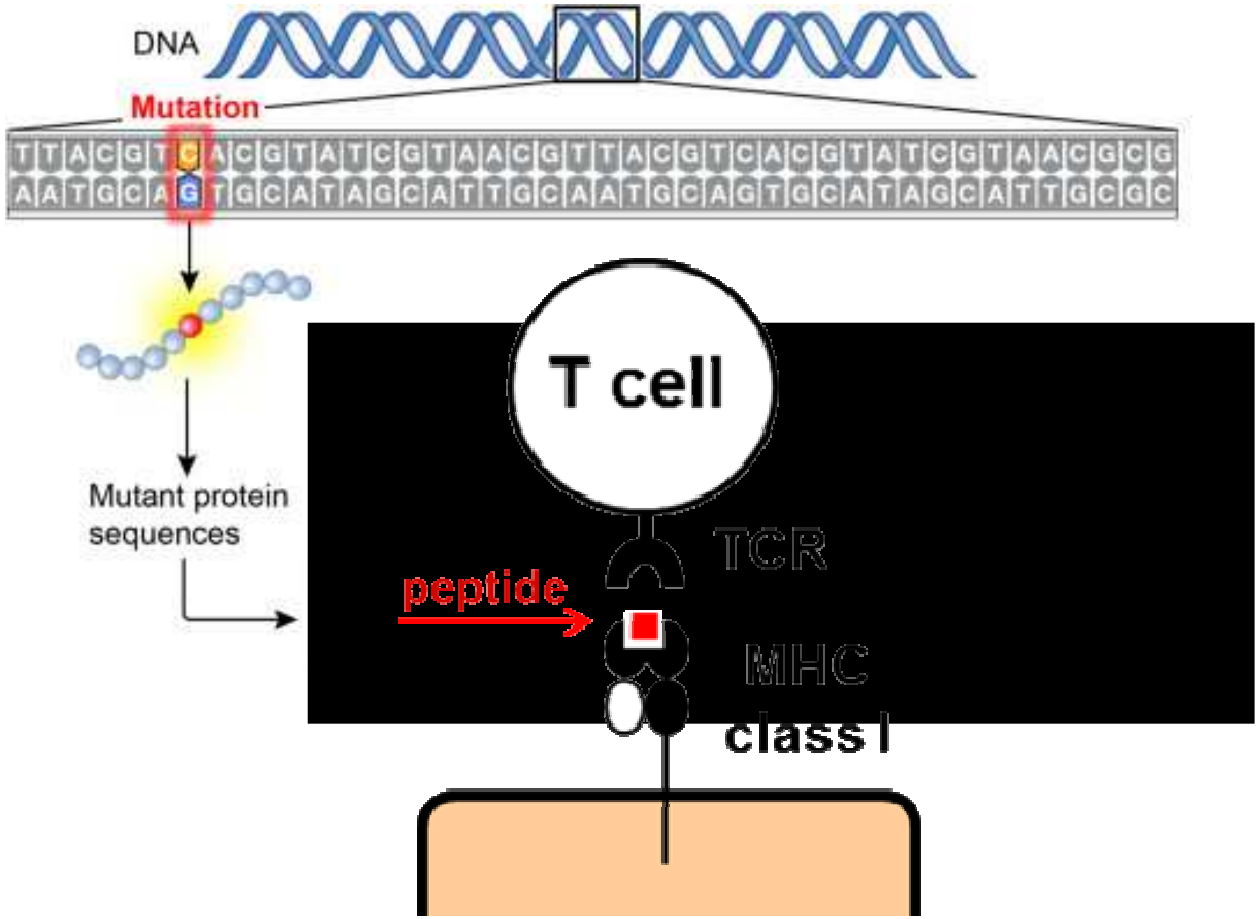




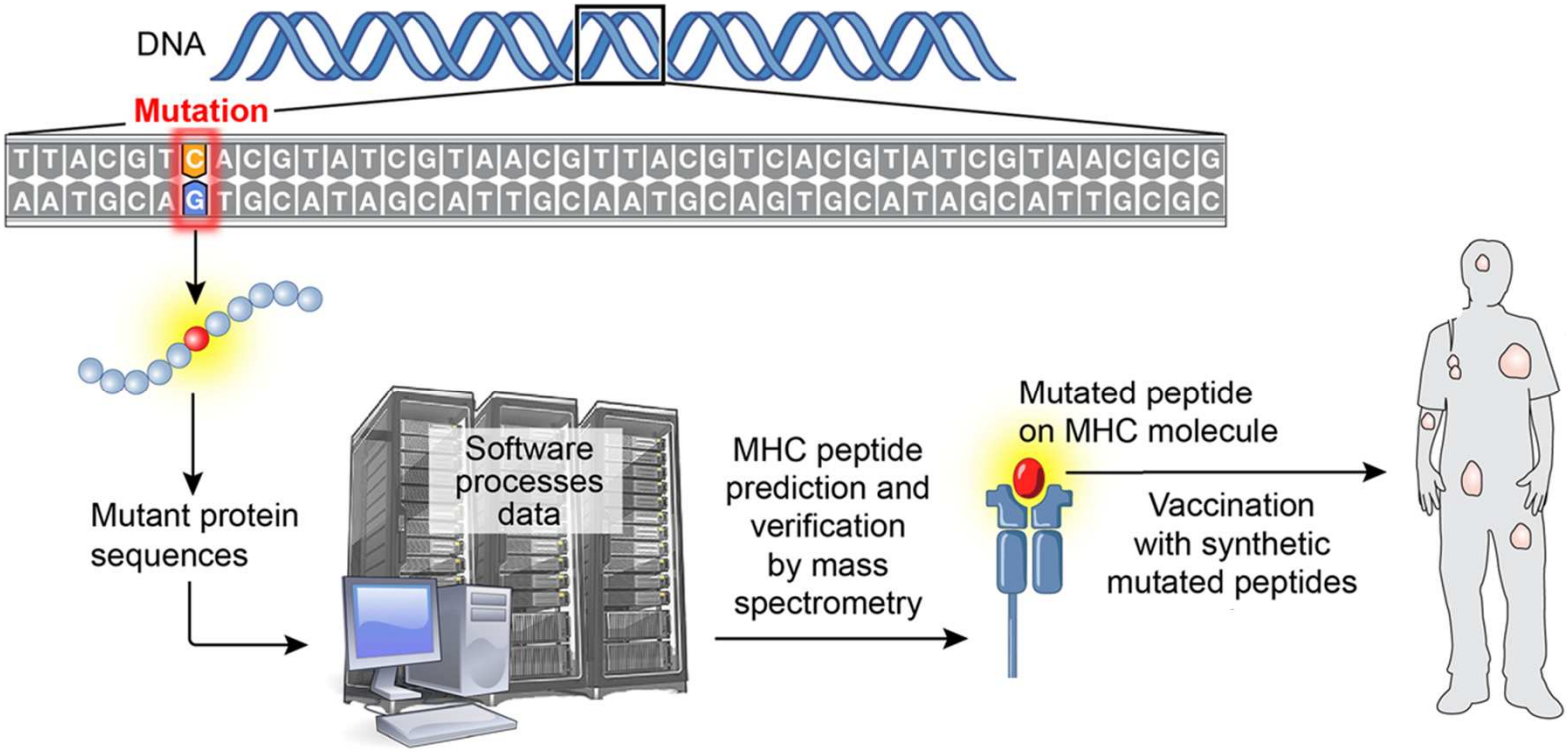
- Neurological toxicities observed (patient 5, 7 & 8)
- Histological consistent with necrotizing leukoencephalopathy, multifocal correlating diffuse white matter damage (MRI images) with sparing of gray matter

Robert A. Morgan, et al. J Immunother. 2013 February ; 36(2): 133–151.

Mutated Peptides as Cancer Antigens



From Mutation to Vaccine: Genetically Engineer & “Amplify” tumor-specific, mutated antigens



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

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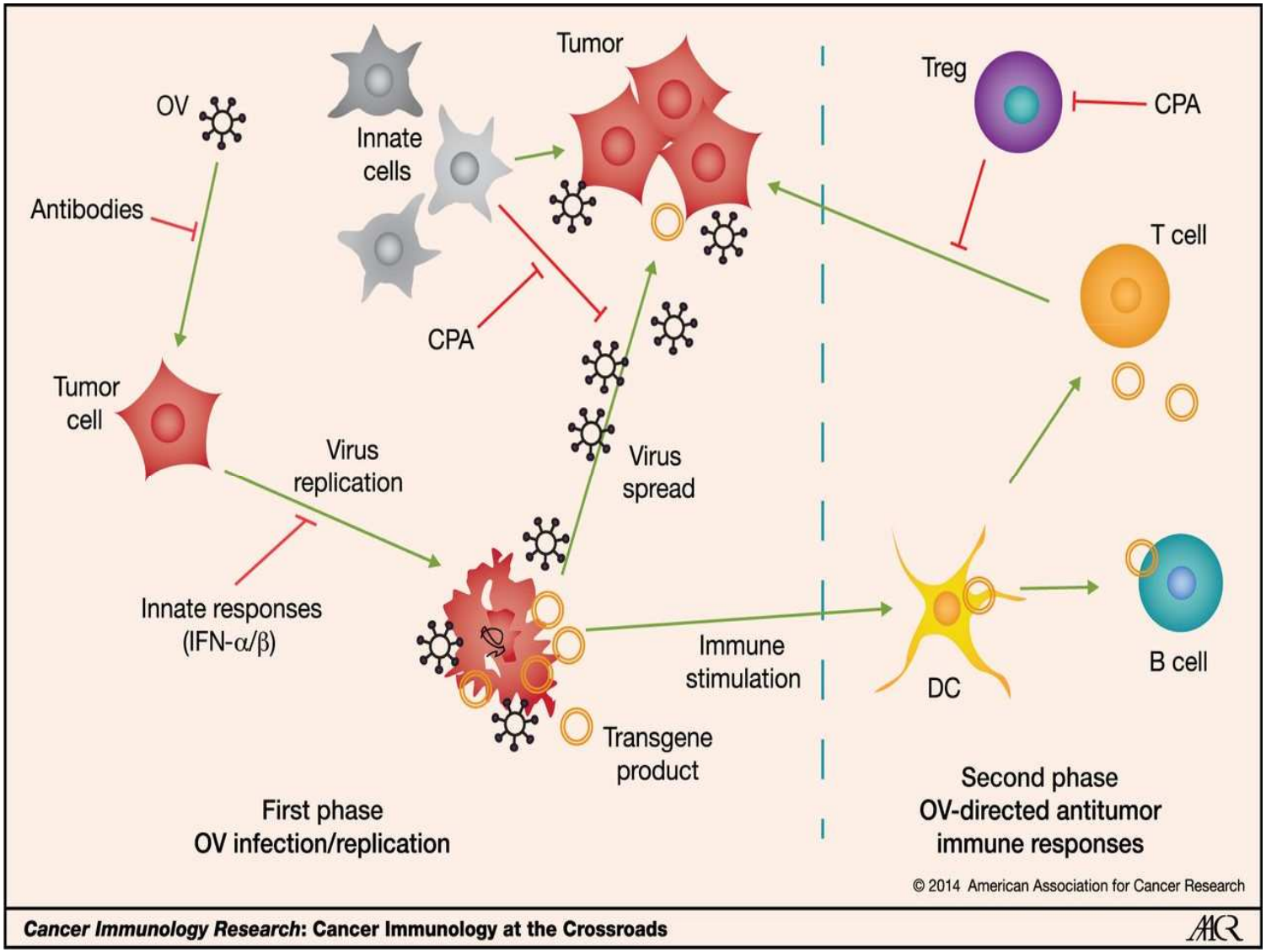
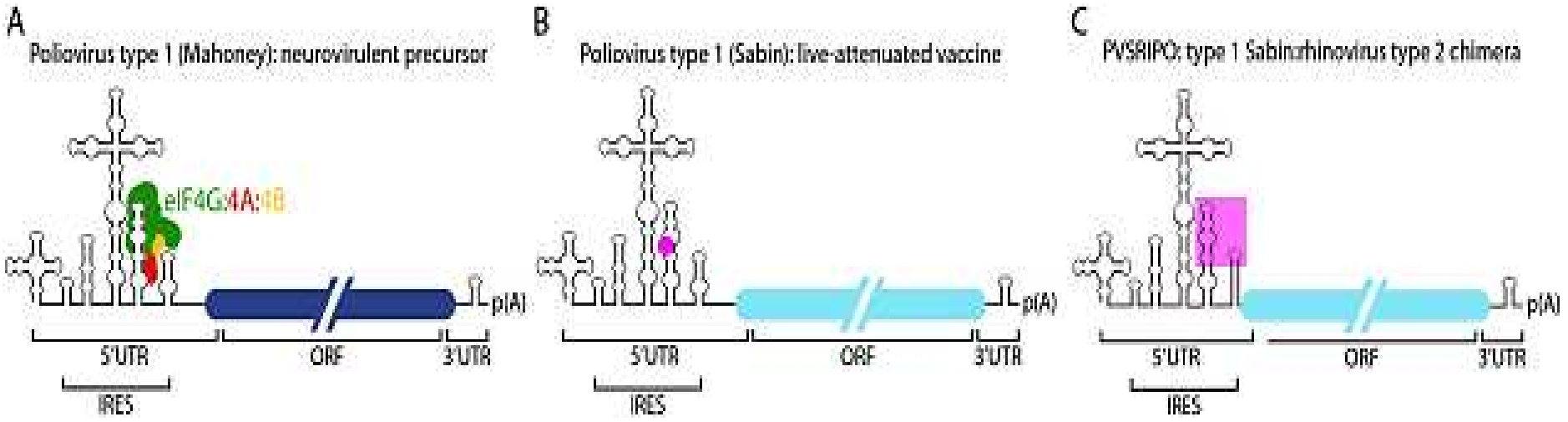
OV-mediated effects in tumor.



E. Antonio Chiocca, and Samuel D. Rabkin Cancer Immunol Res 2014;2:295-300

AACR American Association for Cancer Research
Cancer Immunology Research

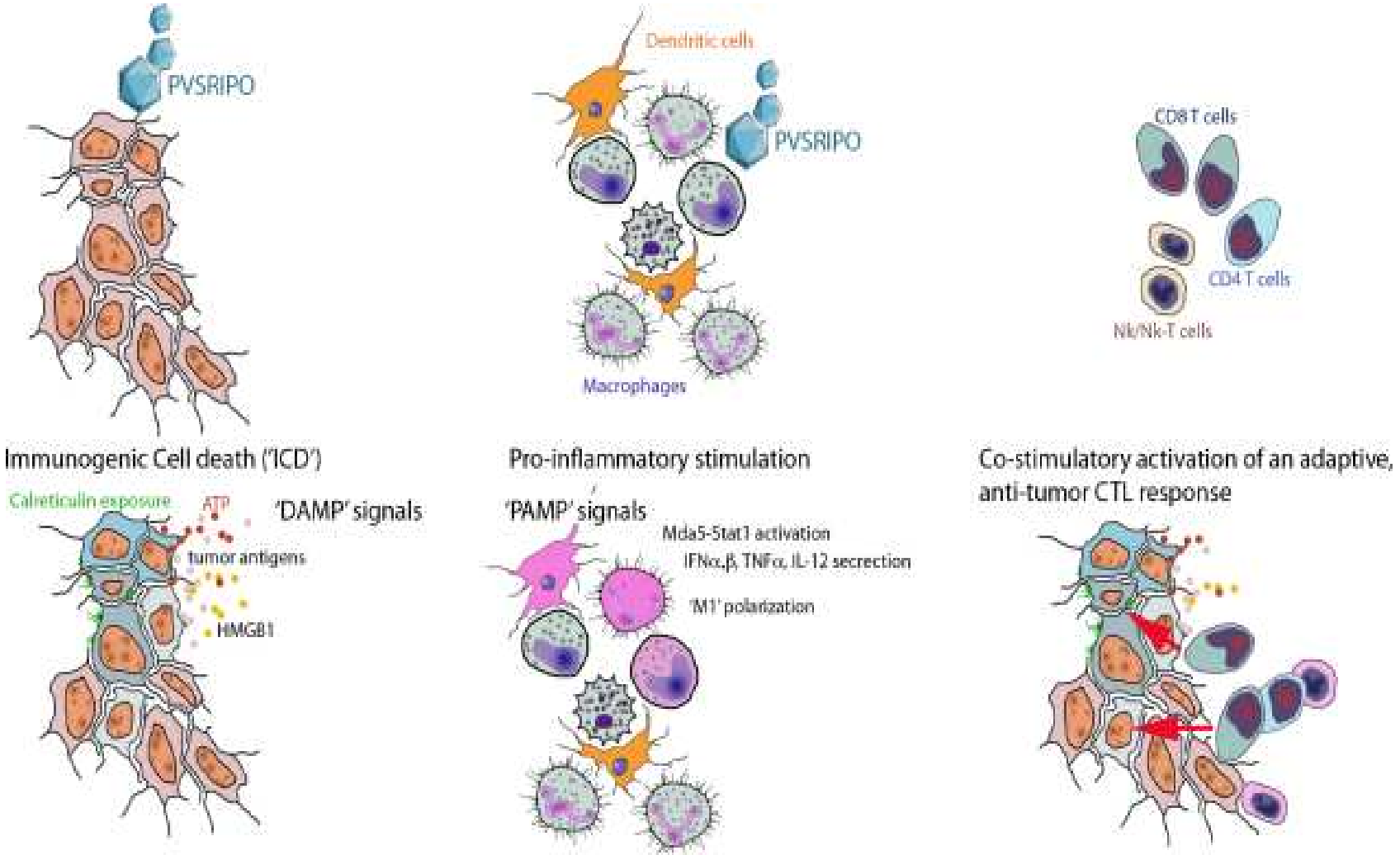
Oncolytic polio virotherapy of cancer



PVS-RIPO (C): a nonpathogenic oncolytic poliovirus recombinant underlying the pre-clinic and clinical development against glioblastoma

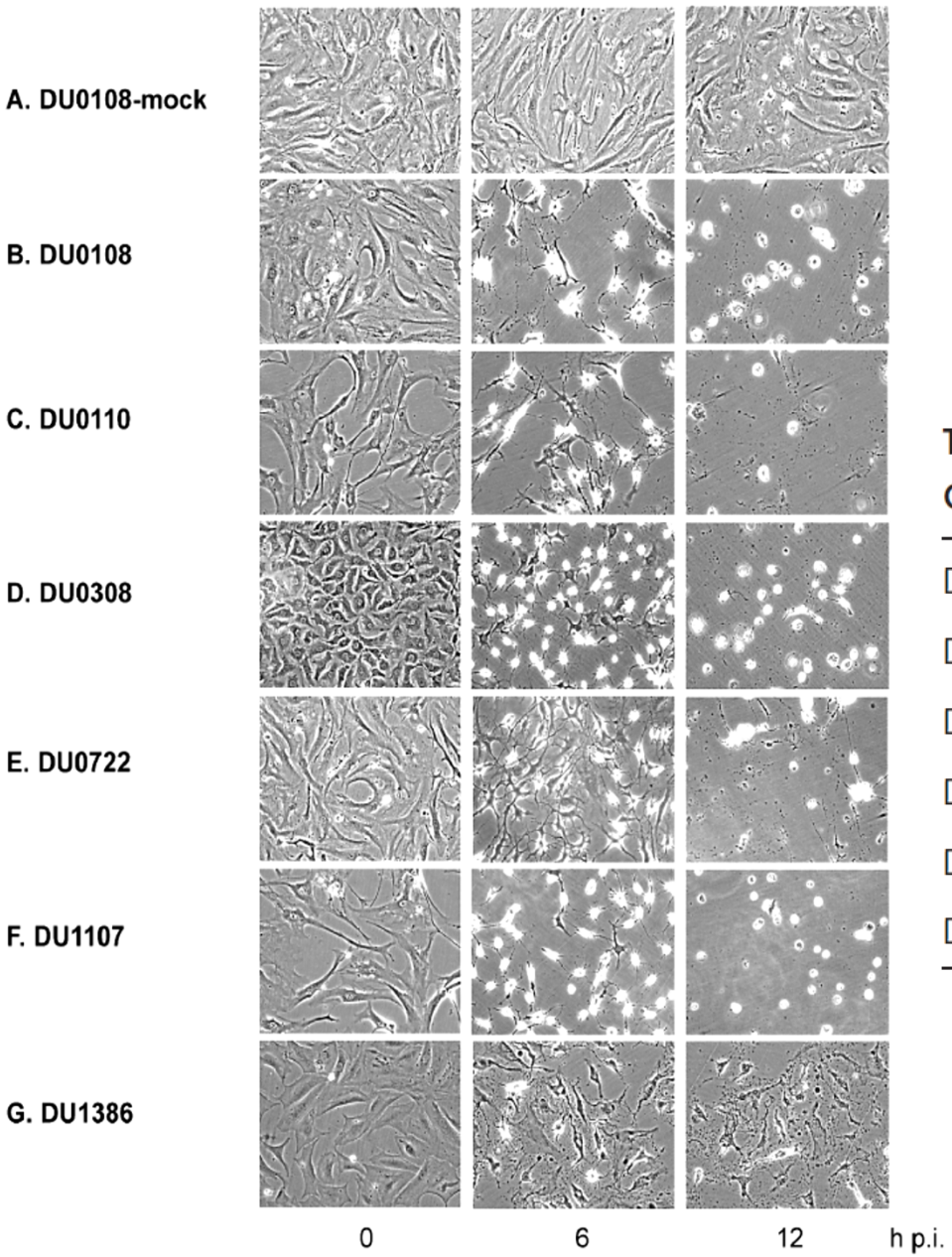
Brown MC., et al. Cancer, 120 (21): 3277-3286, 2014

Oncolytic polio virotherapy of cancer



Brown MC., et al. Cancer, 120 (21): 3277-3286, 2014

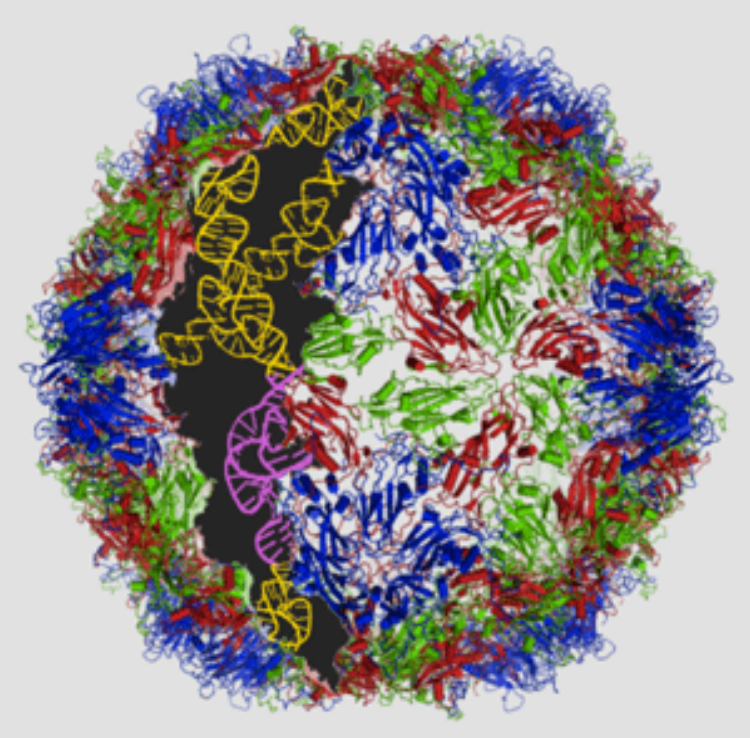
Poliovirus Receptor CD155-targeted Oncolysis of Glioma

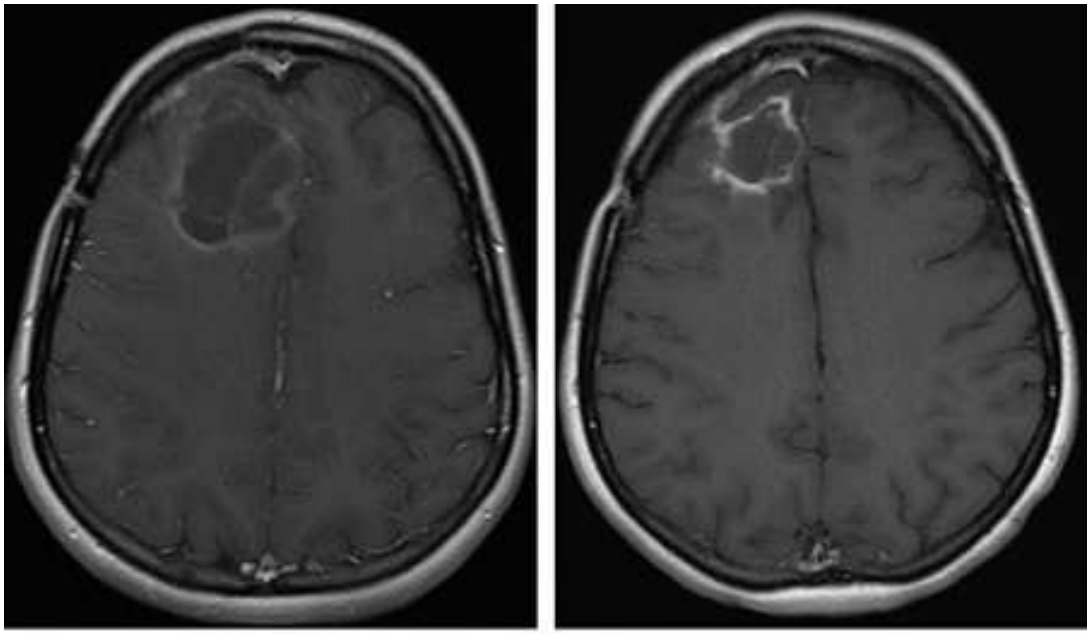


Tumor/ Cell line no.	Location	Histological classification
DU0108	L temporal	Glioblastoma multiforme, grade IV
DU0110	L parietal	Anaplastic astrocytoma, grade III
DU0308	R temporal	Glioblastoma multiforme, grade IV
DU0722	R temporal	Glioblastoma multiforme, grade IV
DU1107	R parietal	Glioblastoma multiforme, grade IV
DU1386	R temporal	Anaplastic astrocytoma, grade III

Merrill, MK, et al. Neuro-Oncol. July 2004

Duke University PVS-RIPO trial Eligibilities: Recurrent glioblastoma patients with only one tumor. The tumor must be surgically accessible; the size must be no smaller than 1 cm and no larger than 5.5 cm, and the tumor must be located at least 1 cm away from the ventricles





Patient treated on PVS-RIPO
2 months after treatment

Same patient treated on PVS-RIPO
9 months after treatment

The structure of the PVS-RIPO virus:
The Virus particle consists of a protein shell (blue, red and green shapes) arranged in a symmetric structure. In this image, the particle has been "cracked open," to reveal the virus genome (yellow, pink), which is surrounded by the protein shell. The PVS-RIPO genetic code is based on the Sabin vaccine (yellow) with a piece of genetic information from a common cold virus spliced in (pink)

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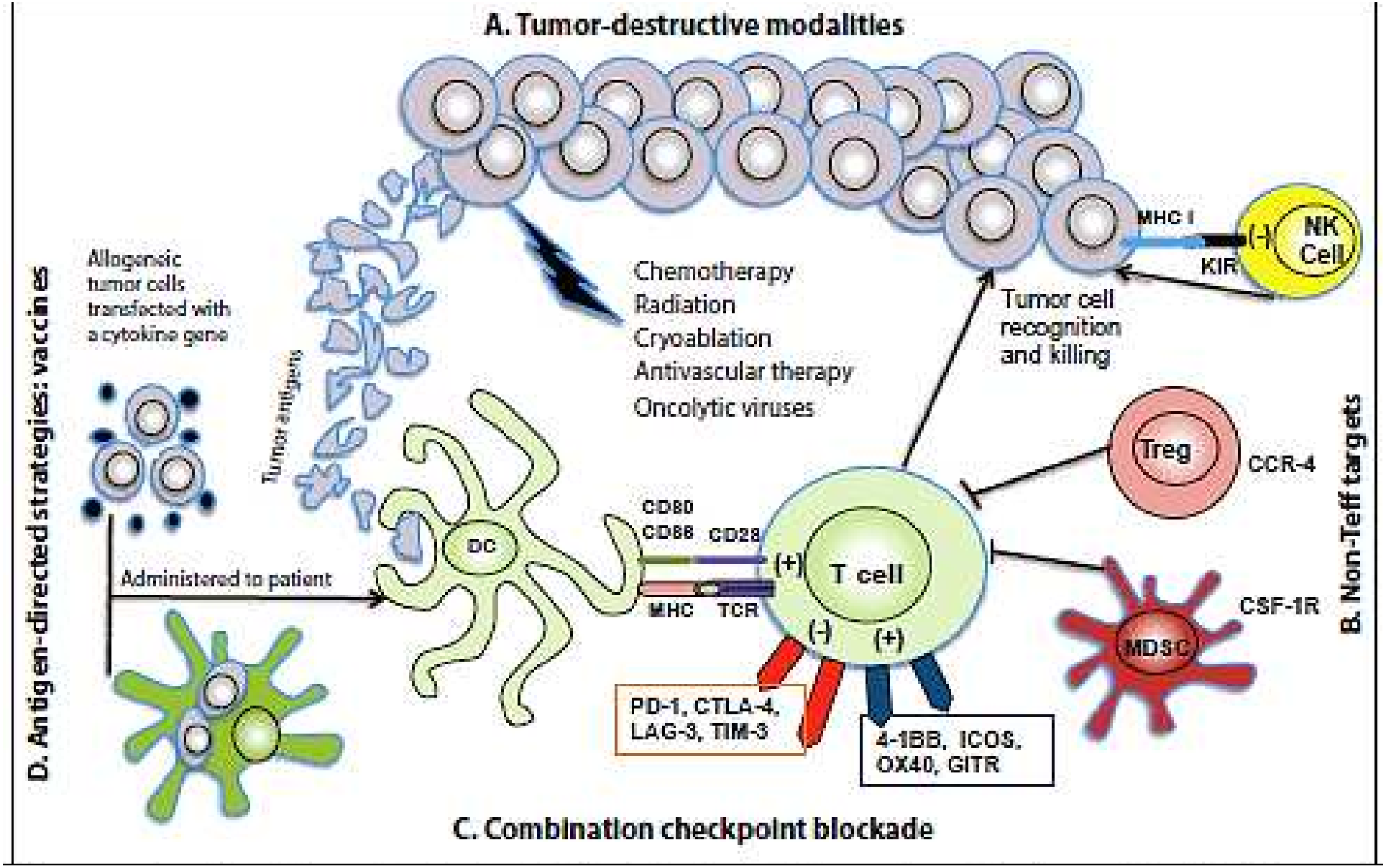


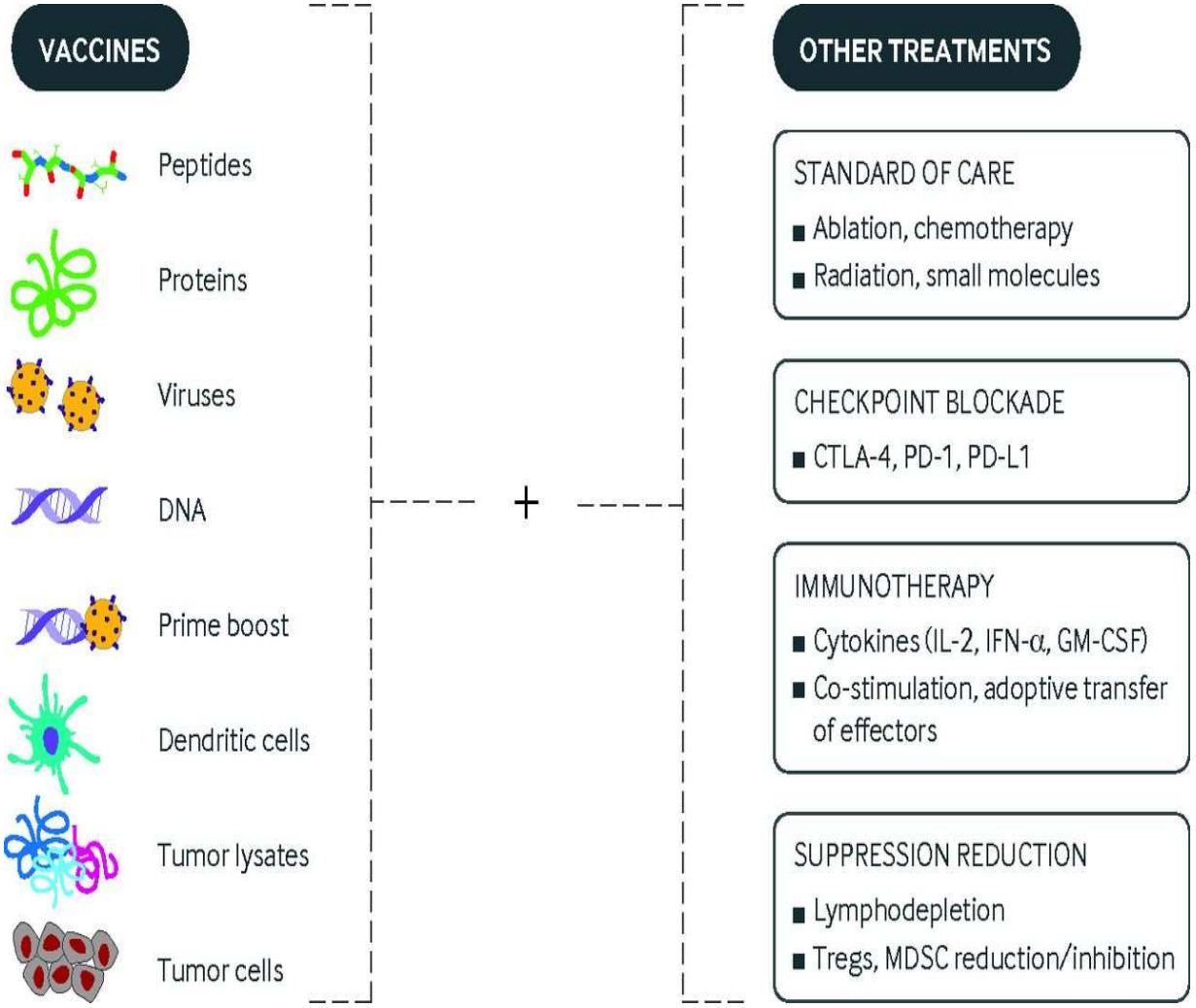
and tumor-specific adaptive immunity; (B) novel targeted agents may inhibit the suppres-

Effects of Radiation on Tumors

Effects on Tumor Microenvironment	RT Dose/Regimen
Enhance antigen uptake and presentation by antigen-presenting cells	Local x-irradiation (10 Gy × 1)
Promote maturation of antigen-specific DCs	Ablative local x-irradiation (20 Gy × 1)
Induction of chemokines by intratumoral DCs to attract effector cells	One dose 10 or 20 Gy applied on cell lines Whole body with a single dose of 1000 rads Ablative local x-irradiation (20 Gy × 1)
Enhanced NK cell function and CXCL16 secretion	γ-irradiation (2.78 Gy/min)
Increase in secretion of immune stimulatory factors that can change tumor cell phenotype	In vitro γ- irradiation (20 Gy)
Increase in intratumoral infiltration by $CD45^+/CD11b^+$ myeloid-derived cells	In vitro (10-25 Gy) over a period of 3 d, and local γ-irradiation of mice (25 Gy)
Enhanced epitope spreading	In vitro ionizing radiation (4.5 Gy/min)
Reduction of tumor mass resulting in increased T-cell infiltration	In vitro ionizing radiation (2-10 Gy) Three distinct regimens of local ionizing radiotherapy (20 Gy × 1, 8 Gy × 3, or 6 Gy × 5 fractions in consecutive days) In vitro radiation at 1 × (0, 2.5, 5, 8, and 16 Gy)
Effects on malignant cells	
Induction of immunogenic cell death	Local irradiation 1 × (15 Gy) or fractionated (5 × 3 Gy)
Enhanced antigen presentation by upregulation of MHC-1 expression	In vitro γ-irradiation (20 Gy) In vitro (10-25 Gy) over a period of 3 d, and local γ-irradiation of mice (25 Gy) One dose 10 or 20 Gy applied on cell lines
Upregulation of TNF-α, IL-1β, GM-CSF, and IL-6 secretion	In vitro x-radiation
Increased expression of tumor-associated antigens	In vitro γ-irradiation (20 Gy)
Upregulation of the death receptor and engagement of the Fas/Fas ligand pathway	In vitro ionizing radiation (4.5 Gy/min)

Wotchok, et al. Am J Clin Oncol, 38: 90-97, 2015

Cancer vaccines can be combined with various other treatments such as standard of care approaches, checkpoint blockade, immunotherapy, and strategies to reduce suppression.



Lisa H Butterfield BMJ 2015;350:bmj.h988

thebmj

Summary & Conclusions

- Oncolytic viruses (OVs) can selectively replicate, thereafter, kill cancer cells with minimal risk of harming normal tissue
- Oncolytic viruses (OVs) can effectively induce immune response to themselves and to the infected tumor cells
- Oncolytic viruses (OVs) can be genetically engineered
  - Nonpathogenic
  - Armed with immunomodulatory transgenes
- Oncolytic viruses (Ovs) provides a diverse platform for immunotherapeutic research and potentials for their clinical applications
- Cancer vaccines are both important in cancer preventions and therapies
- Cancer-specific immunity depends on
  - Balance between host immunostimulation and immunosuppression
  - The presence of tumor-specific antigen (neo-antigen)
  - Mutation load and level of each neo-antigen expression
  - Other factors

Thank You !!!

Questions:

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Back up Slides

Peptide-based Cancer Vaccines

The NEW ENGLAND JOURNAL of MEDICINE

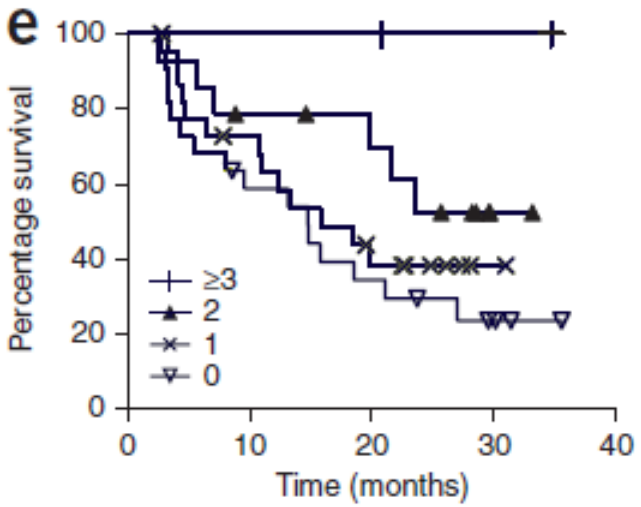
ORIGINAL ARTICLE

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



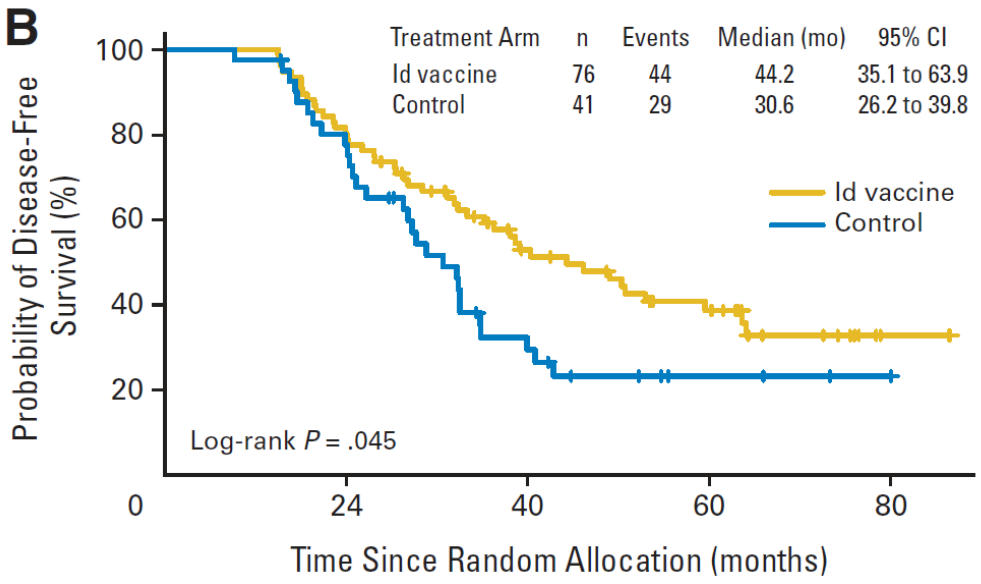
nature medicine AUGUST 2012

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

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JOURNAL OF CLINICAL ONCOLOGY

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

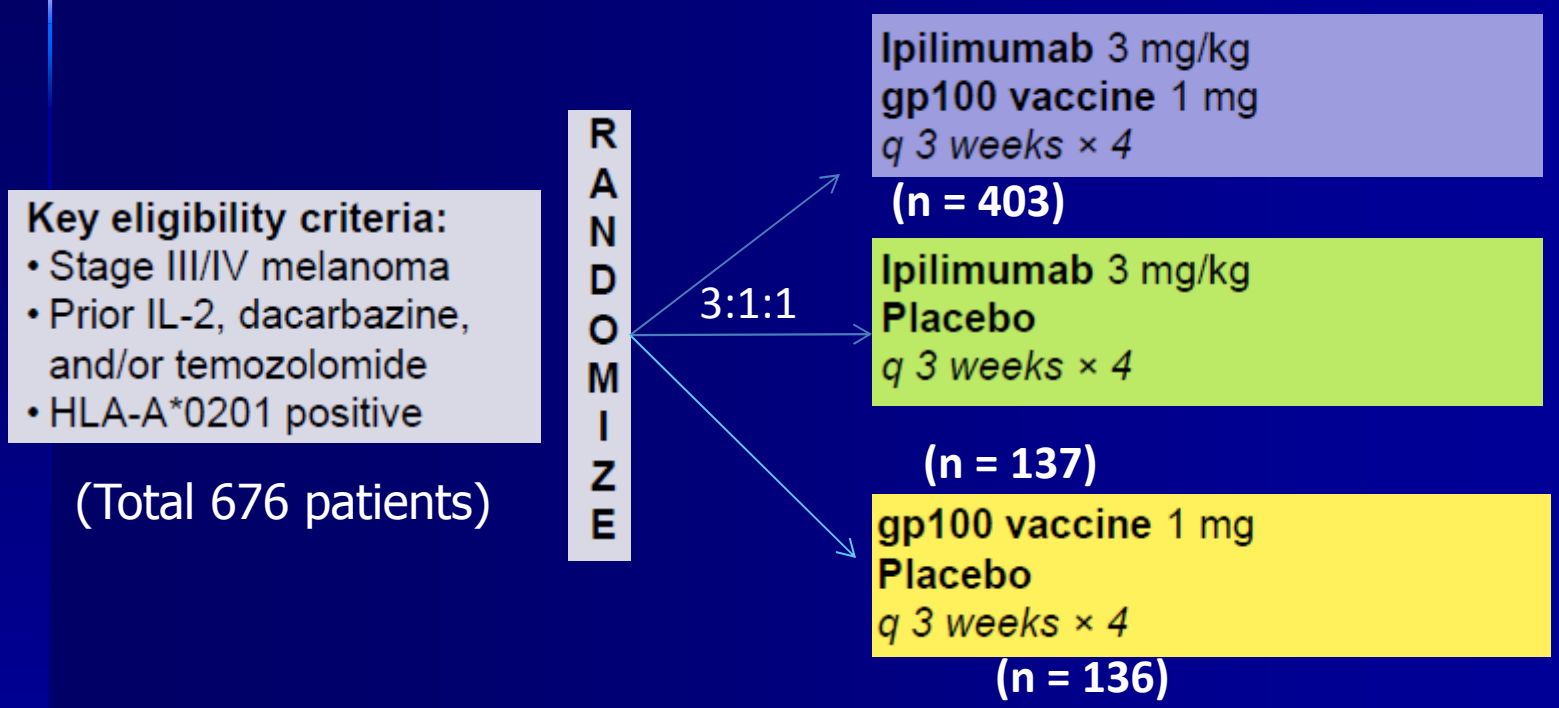
Stage IV and locally advanced stage III melanoma patients

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

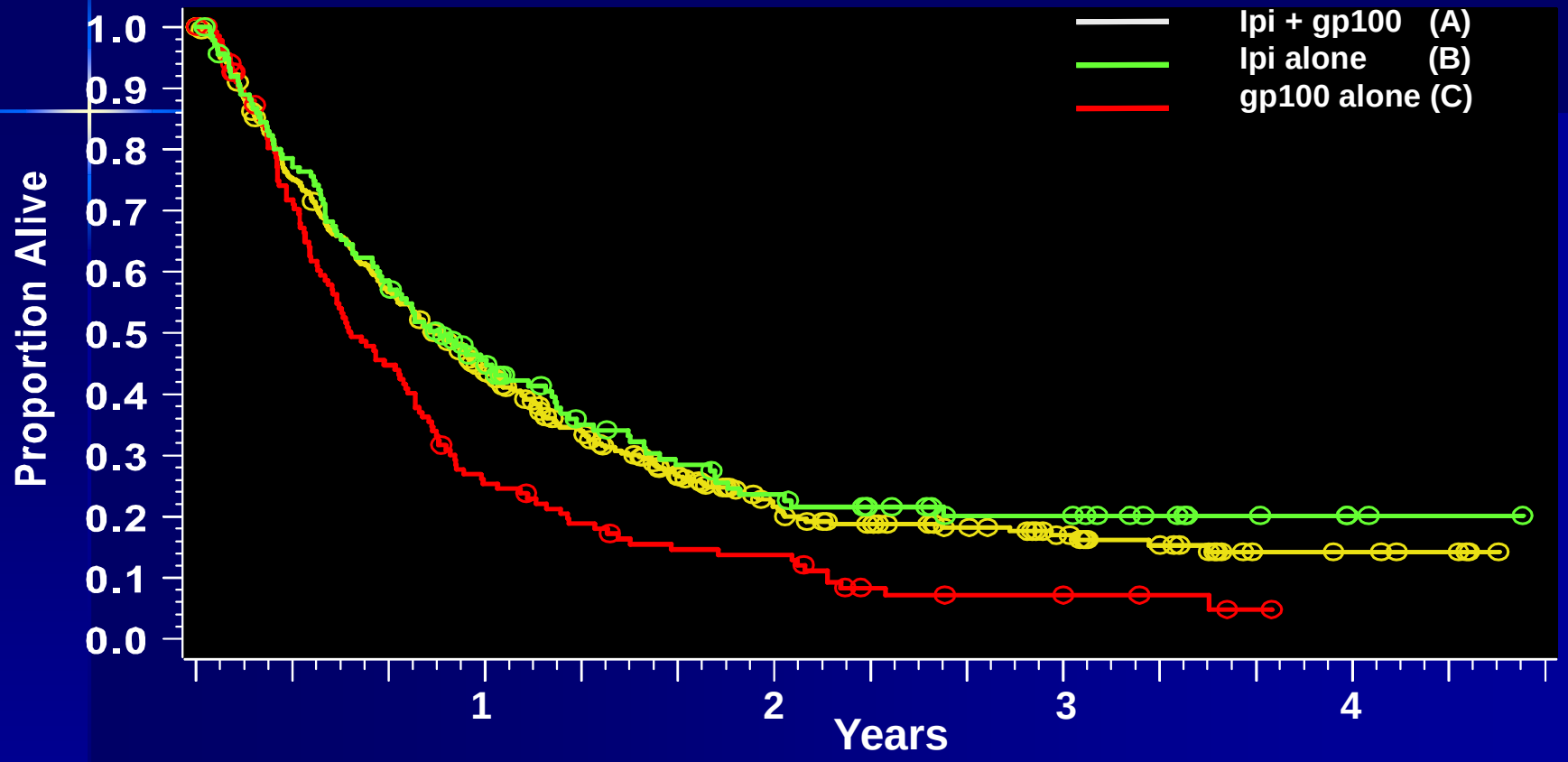
Phase III Trial of Ipilimumab Plus gp100 Vaccine Versus gp100 Vaccine Versus Ipilimumab as Second-line Therapy in Advanced Melanoma: Treatment Schema



Primary endpoint: best ORR (original), changed to OS before unblinding/analysis
Secondary endpoints include: best ORR, duration of response, PFS, TTP

Hodi FS et al. N Engl J Med 2010;363:711-723

Ipilimumab Improves Overall Survival compared to control



Survival Rate	Ipi + gp100 N=403	Ipi + pbo N=137	gp100 + pbo N=136
1 year	44%	46%	25%
2 year	22%	24%	14%

Hodi FS et al. N Engl J Med 2010;363:711-723