Advances in Immunotherapy-NC

Cancer Vaccines

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Disclosures

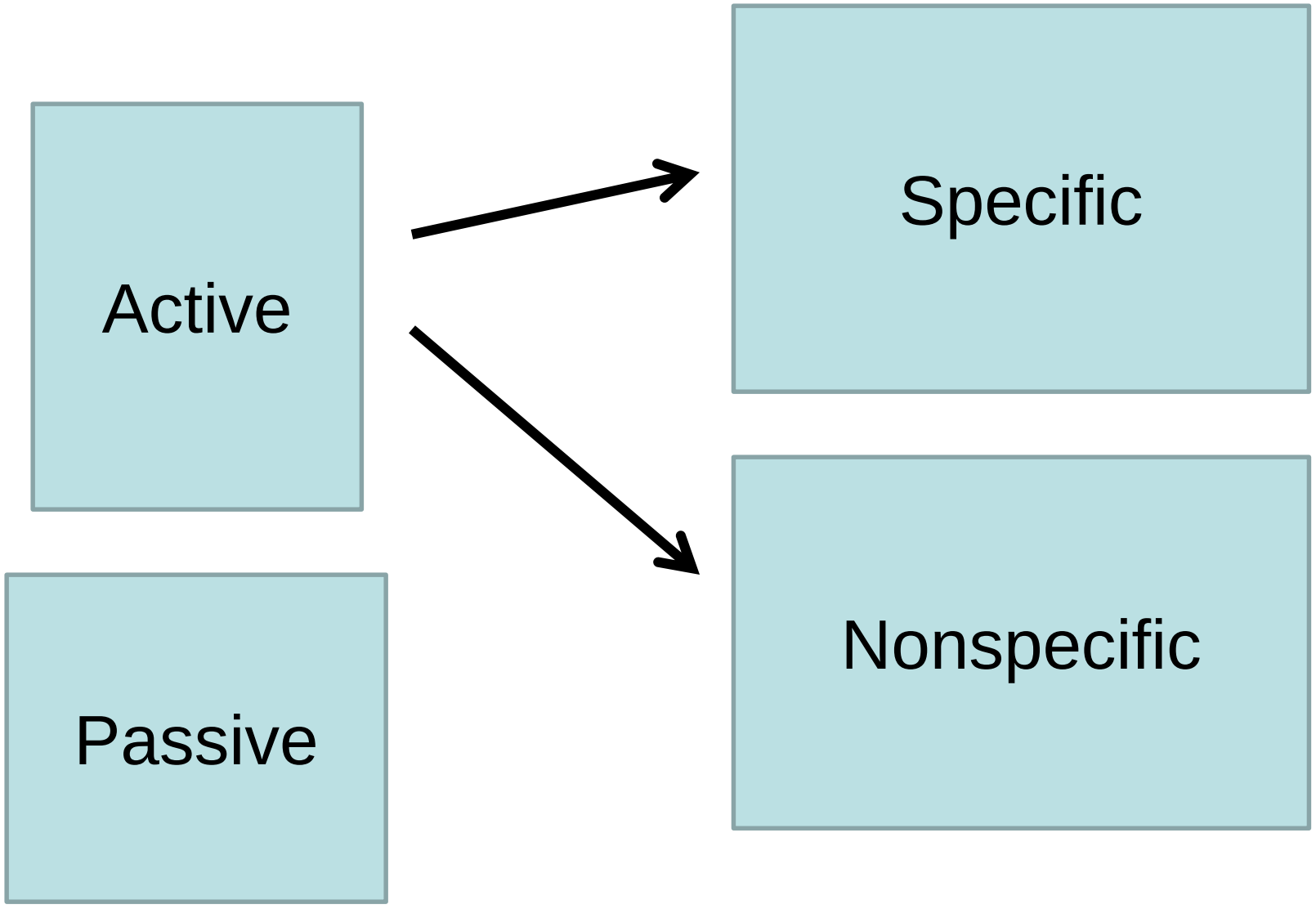
- Related Research support: Alphavax, Etubics, Aduro, Precision Biologics, Newlinks, BMS

Overview of lecture

- Background on rationale and biologic mechanism of cancer vaccines
- Tumor antigens
- Vaccine strategies
- Measuring immune responses to Vaccines
- Summary

BACKGROUND ON RATIONALE AND BIOLOGIC MECHANISM OF CANCER VACCINES

Immunotherapy



Vaccine

- (n): medical : a substance that is usually injected into a person or animal to protect against a particular disease

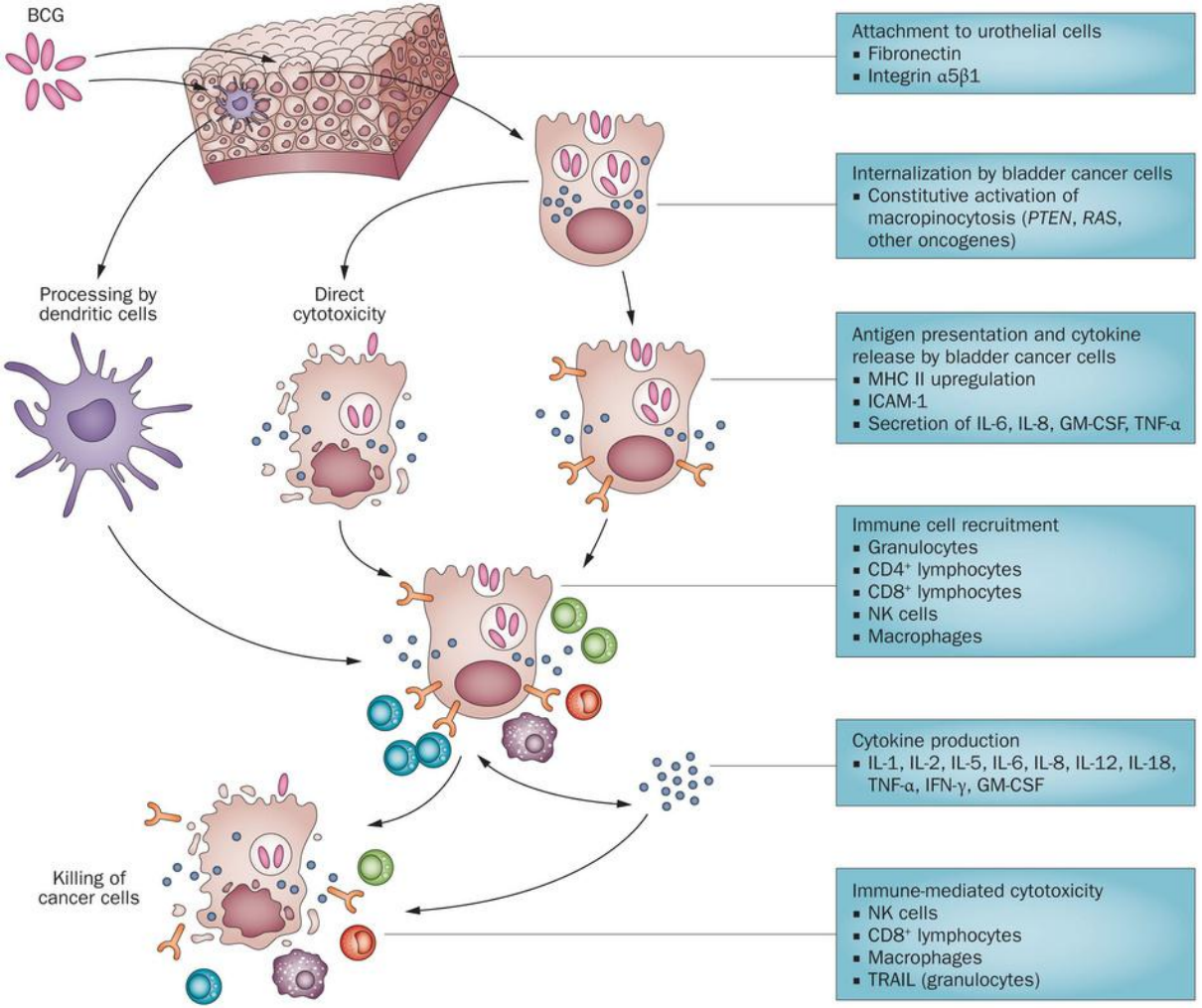
Therapeutic vaccine: Treat an existing disease

http://www.merriam-webster.com/dictionary/vaccine

The first active (nonspecific) immunotherapy?

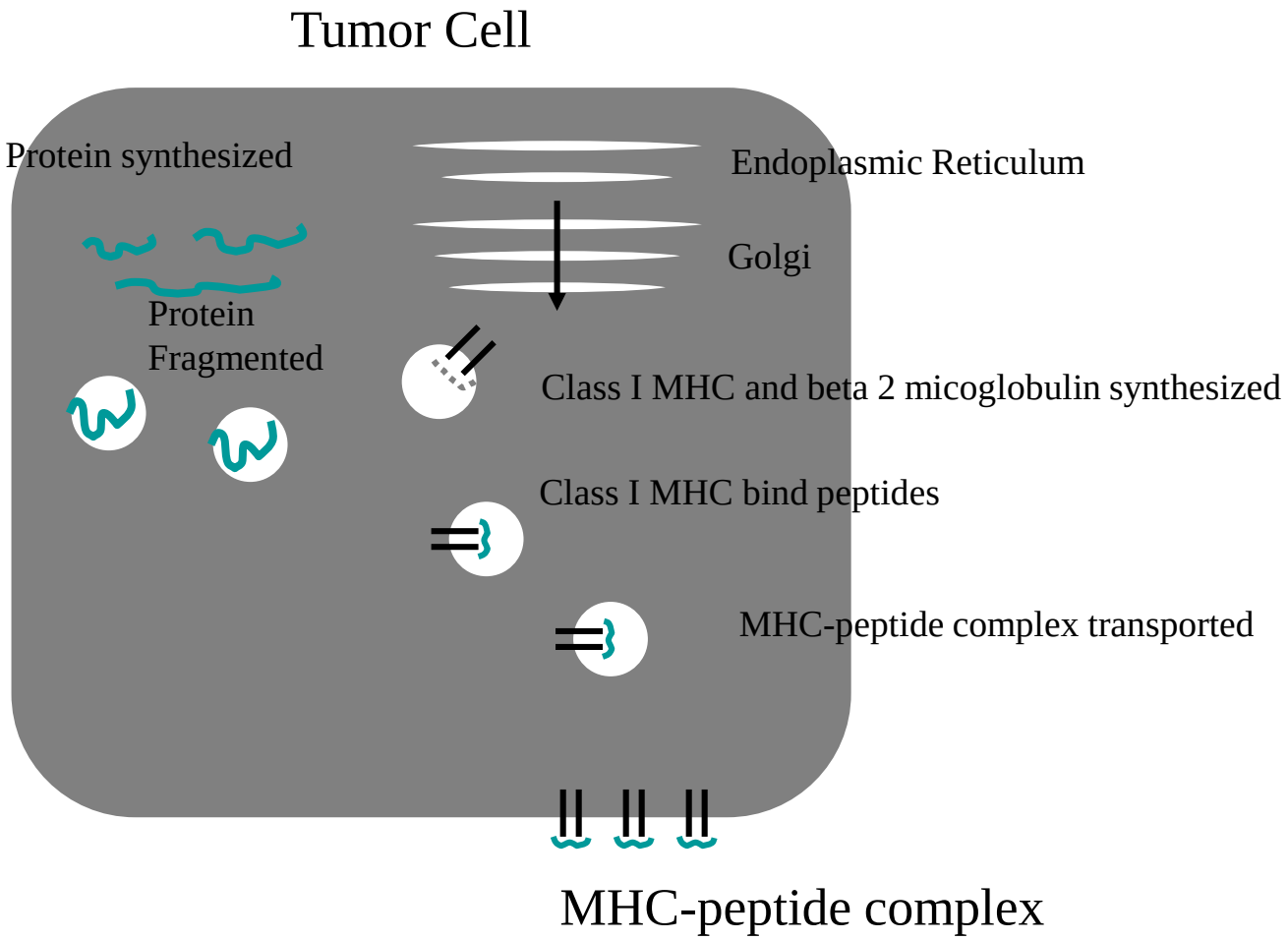
Coley, William B. "A Preliminary Note on the Treatment of Inoperable Sarcoma by the Toxic Product of Erysipelas." *Post-graduate* 8:278-86, 1893.

Bacillus Calmette–Guérin: Non-specific immunotherapy

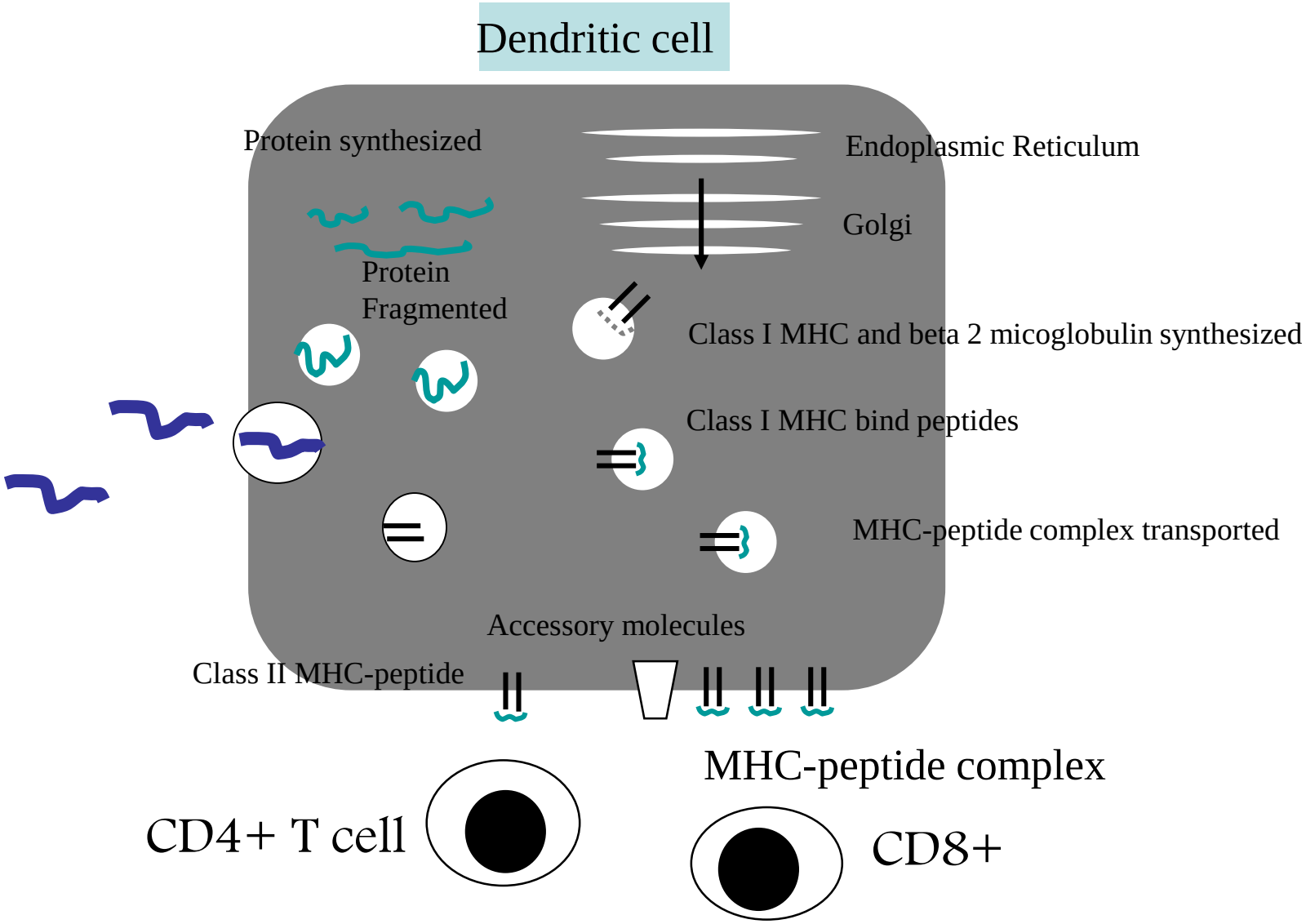


Redelman-Sidi G et al, Nature Reviews Urology, 2014, 11: 153-62.

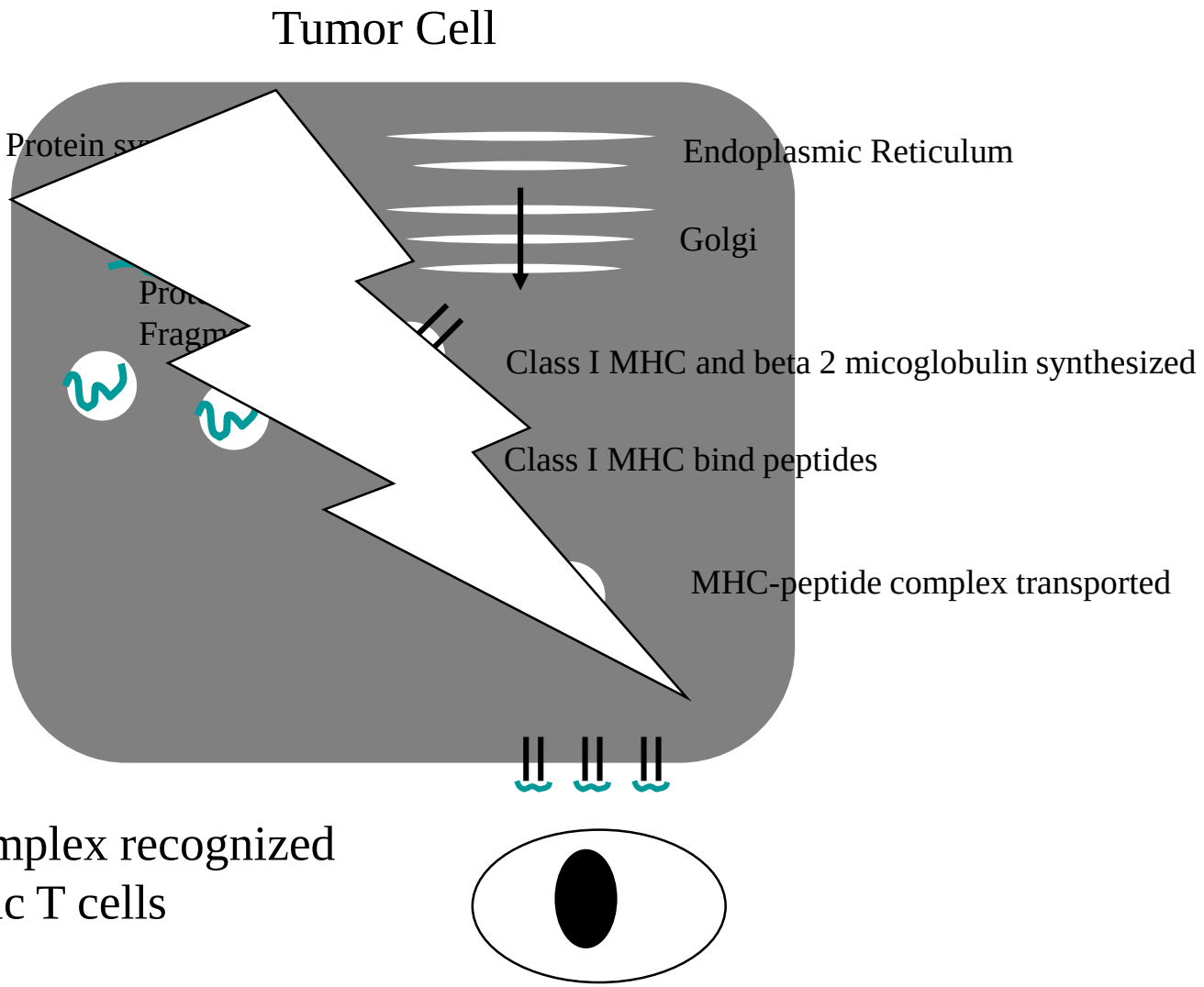
Problem: Tumors do not have necessary machinery to activate immune system by themselves



Cross presentation of antigen:
Goal of vaccines is to direct antigen to dendritic cells

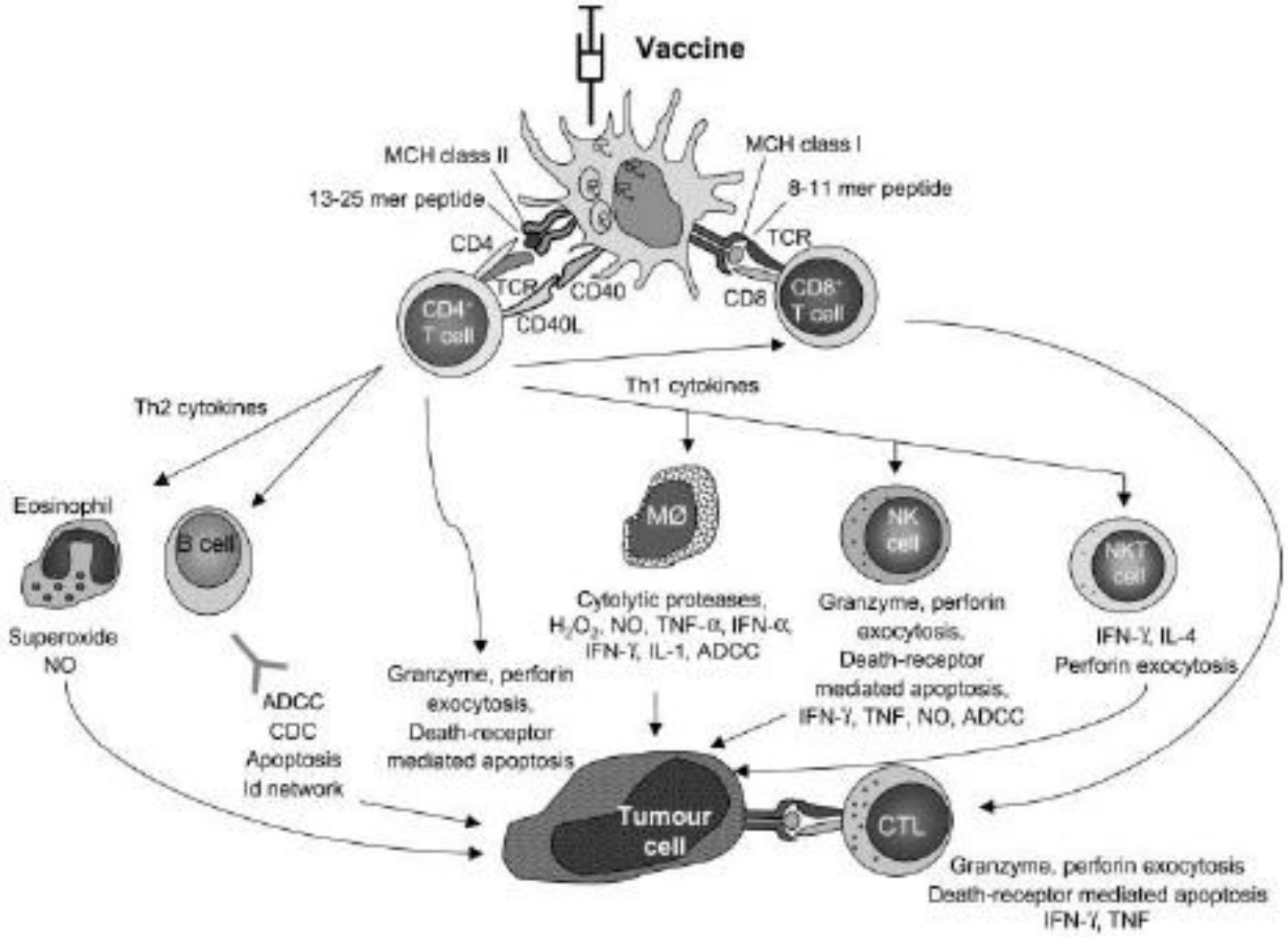


Once activated, T cells can destroy tumor targets without co-stimulatory signals



MHC-peptide complex recognized by antigen specific T cells

Mechanism of tumor vaccines



Mosolits, **Annals of Oncology, Online**

TUMOR ANTIGENS

Types of tumor antigens

- Tumor specific
  - Unique to tumor
  - essential for tumorigenesis/ cancer progression
  - caused by somatic mutation
  - not found on any normal adult somatic tissues
  - Personalized
- Tumor-associated
  - appear on various cancer and normal cells, though with different expression levels.

NCI prioritization of cancer antigens

- therapeutic function
- Immunogenicity
- specificity
- oncogenicity
- expression level
- percentage of positive cells
- stem cell expression,
- # of patients with antigen + cancers
- number of epitopes
- cellular location of expression

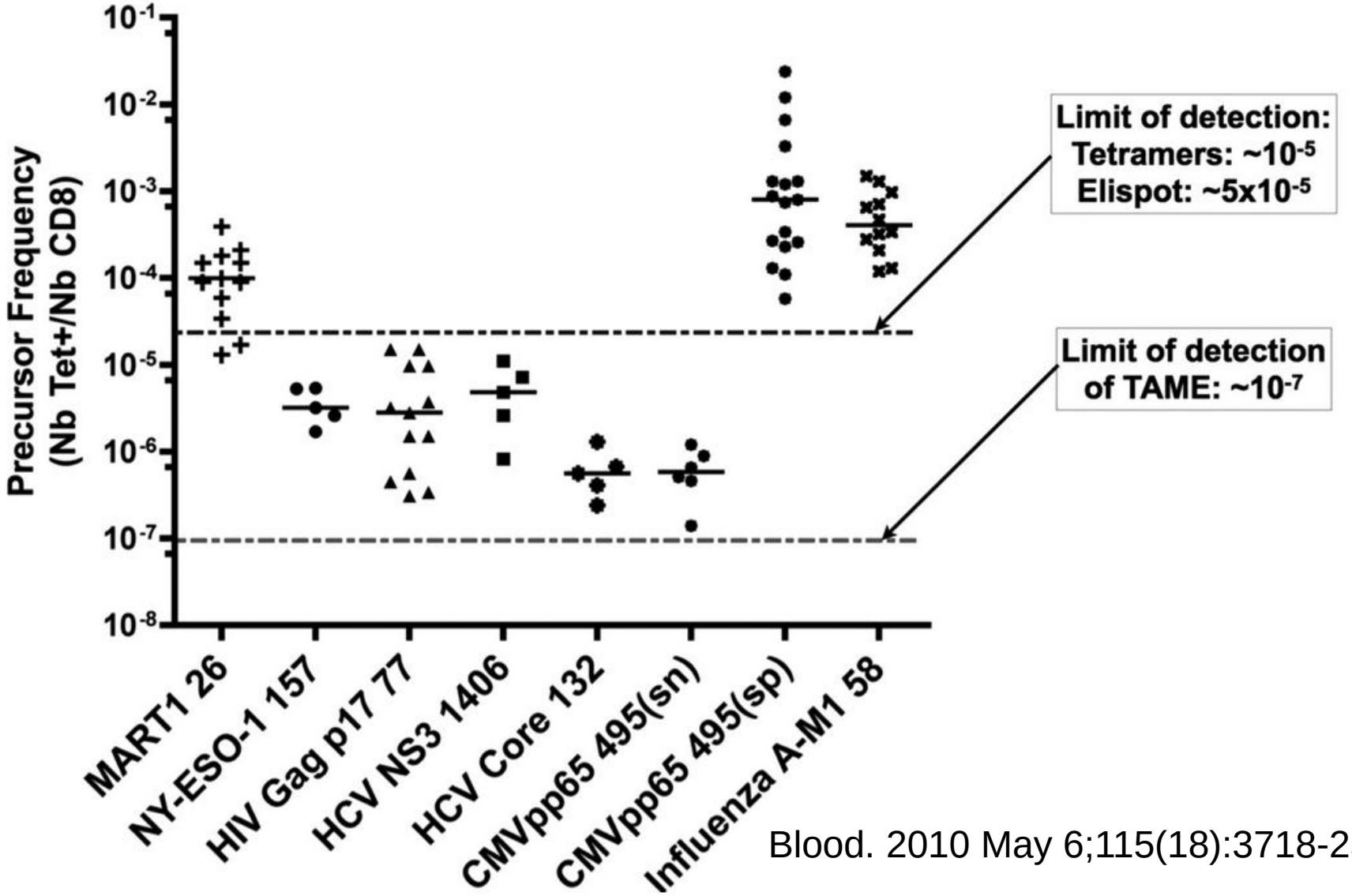
Examples of Tumor Antigens

- Lymphoma—Id protein
- Melanoma— MAGE antigens, Mart-1, gp 100, tyrosinase
- GI—CEA, *ras,* p53
- Breast—targeting CEA, Her-2/*neu,* p53
- Prostate — PSA, PSA-M
- Lung- CEA, MAGE
- Telomerase
- Endothelial antigens
- Proteins related to resistance mechanisms
- Autologous antigens

Debates regarding tumor antigen

- Defined or undefined antigen
  - Well characterized tumor antigens or use “extracts” from tumor
- If defined: one or multiple antigens
  - Role of epitope spreading
- If defined: Class I alone or class I and class II
- If defined: HLA restricted or unrestricted

Challenge to specific immunotherapy: Precursor frequencies are low



Blood. 2010 May 6;115(18):3718-25

VACCINE STRATEGIES

Direct tumor injection: Oncolytic viruses

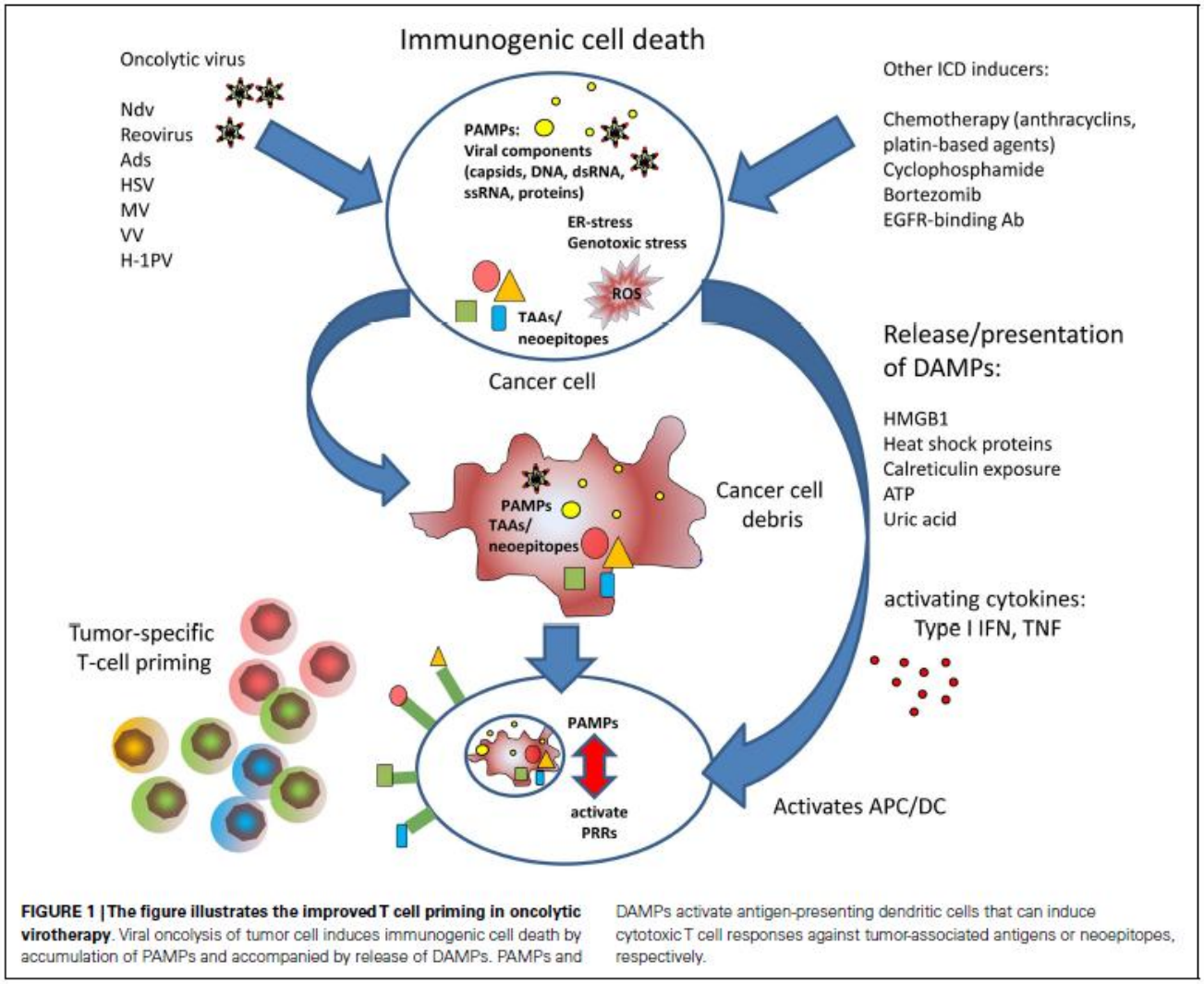
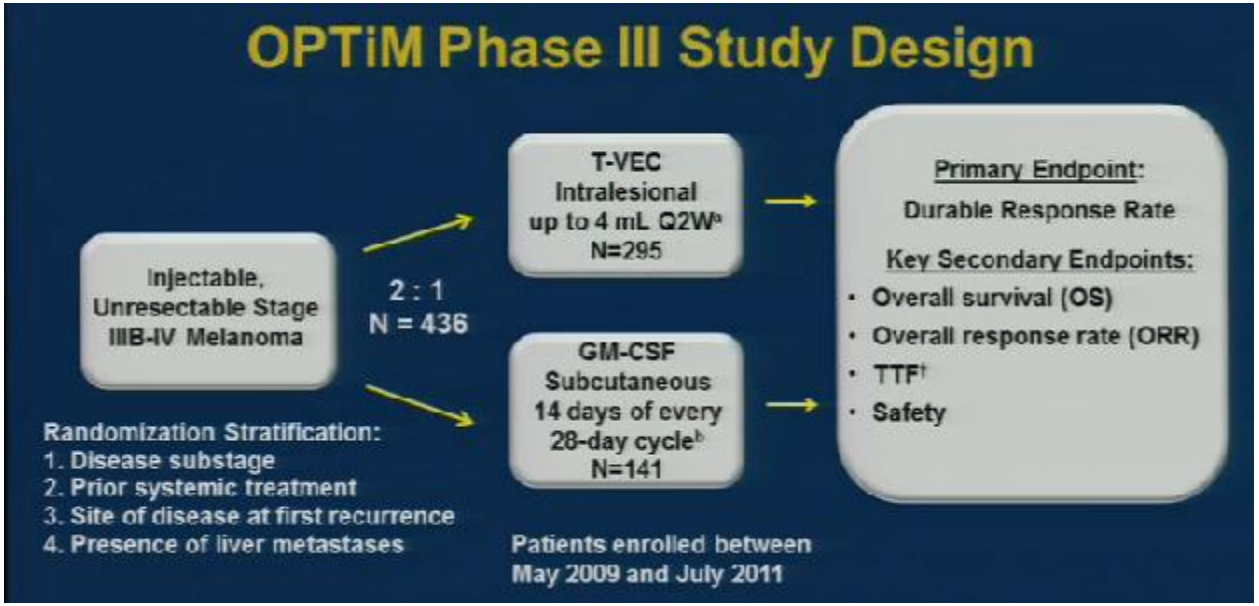


FIGURE 1 | The figure illustrates the improved T cell priming in oncolytic virotherapy. Viral oncolysis of tumor cell induces immunogenic cell death by accumulation of PAMPs and accompanied by release of DAMPs. PAMPs and DAMPs activate antigen-presenting dendritic cells that can induce cytotoxic T cell responses against tumor-associated antigens or neoepitopes, respectively.

Woller, Front Oncol. 2014 Jul 21;4:188.



Overall Response Rate

ITT Set	GM-CSF (N=141)	T-VEC (N= 295)	Treatment Difference (T-VEC – GM-CSF)
Overall Response Rate (95% CI)	5.7% (1.9, 9.5)	26.4% (21.4, 31.5)	20.8% (14.4, 27.1) $P < 0.0001$[a] descriptive
CR	0.7%	10.8%	
PR	5.0%	15.6%	

Durable Response Rate (Primary Endpoint)

ITT Set	GM-CSF (N=141)	T-VEC (N= 295)	Treatment Difference (T-VEC – GM-CSF)
Durable Response Rate	2.1%	16.3%	14.1% 95% CI: (8.2, 19.2) $P < 0.0001$[a]

All responses presented are per independent EAC. Overall responses were not required to be confirmed.
[a]Unadjusted Fisher's exact test

Andtbacka et al. ASCO 2013; LBA9008

Kaufman ASCO2014; Abst 9008a

Table 1. Clinical trials recently launched to evaluate the safety and efficacy of oncolytic virotherapy in cancer patients*

Virus	Indication(s)	Phase	Status	Route	Notes	Ref.
CG0070	Bladder carcinoma	I	n.a.	Intravesical	As a single agent	NCT00109655
ColoAd1	Colorectal carcinoma	I	Recruiting	i.t. or i.v.	As a single agent	NCT02053220
	Ovarian carcinoma	I/II	Not yet recruiting	i.p.	As a single agent	NCT02028117
	Solid tumors	I/II	Recruiting	i.v.	As a single agent	NCT02028442
CVA21	Solid tumors	I	Not yet recruiting	i.v.	As a single agent	NCT02043665
DNX2401	Glioblastoma	I	Recruiting	i.t.	Combined with temozolomide and/or surgery	NCT01956734
HSV-1716	Glioma	I	Recruiting	Into the tumor resection cavity	Combined with dexamethasone and surgery	NCT02031965
ICOVIR-5	Melanoma	I	Recruiting	i.v.	As a single agent	NCT01864759
	Solid tumors	I/II	Recruiting	i.p. (via MSCs)	As a single agent	NCT01844661
MV-NIS	HNSCC	I	Recruiting	i.t.	As a single agent	NCT01846091
	Ovarian carcinoma	I/II	Not yet recruiting	i.p. (via MSCs)	As a single agent	NCT02068794
Pexa-Vec	Ovarian carcinoma	II	Not recruiting	i.v.	As a single agent	NCT02017678
T-vec	Melanoma	II	Not yet recruiting	i.t.	As a single agent	NCT02014441
Toca 511	Brain tumors	I	Recruiting	i.v.	Combined with 5-FC	NCT01985256
VCN-01	Pancreatic cancer	I	Recruiting	i.t.	Combined with gemcitabine	NCT02045589
	Solid tumors	I	Recruiting	i.v.	Combined with gemcitabine	NCT02045602

Pol, OncoImmunology 3, e28694

Intratumoral injection of immunostimulatory genes

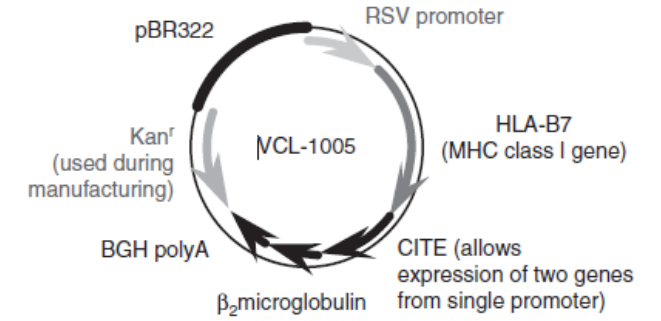
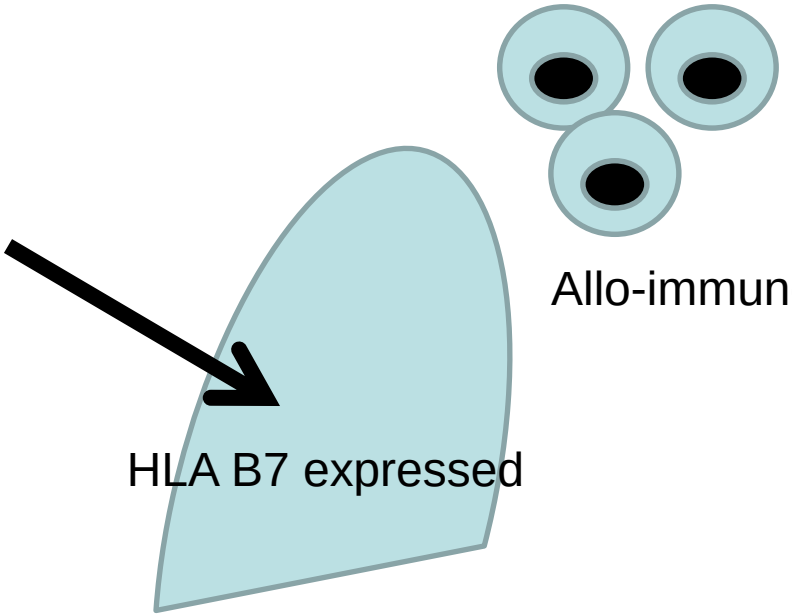
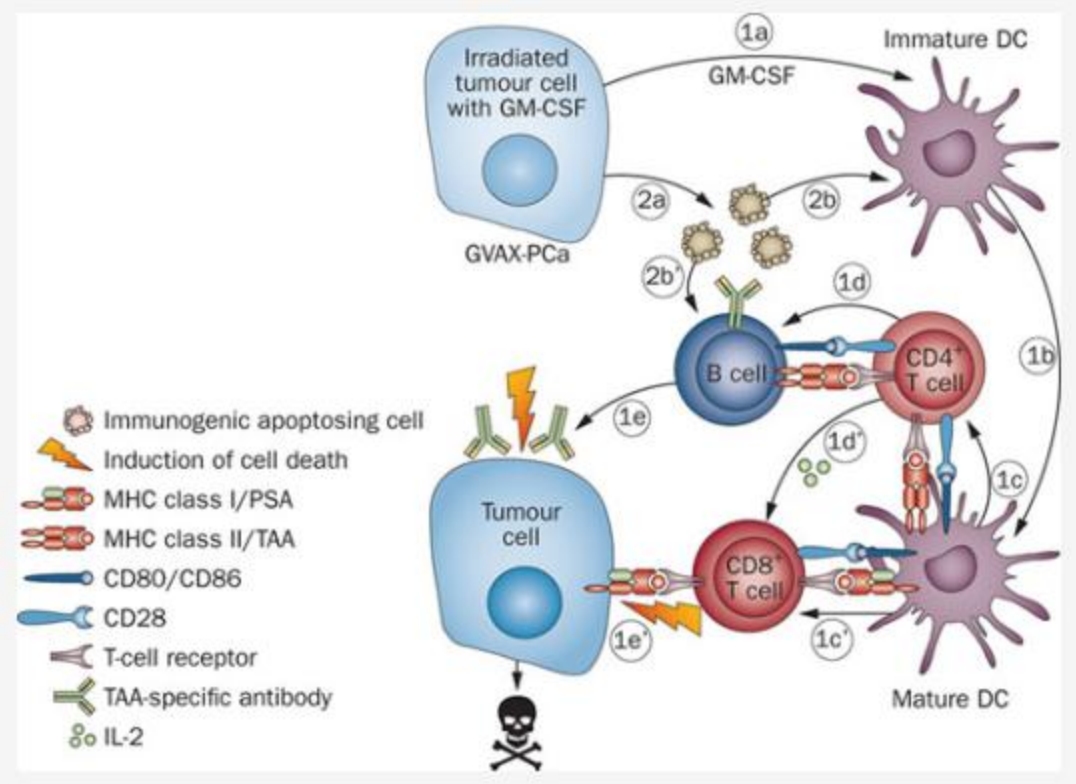


Figure 1. Velimogene aliplasmid: diagram of the plasmid map.



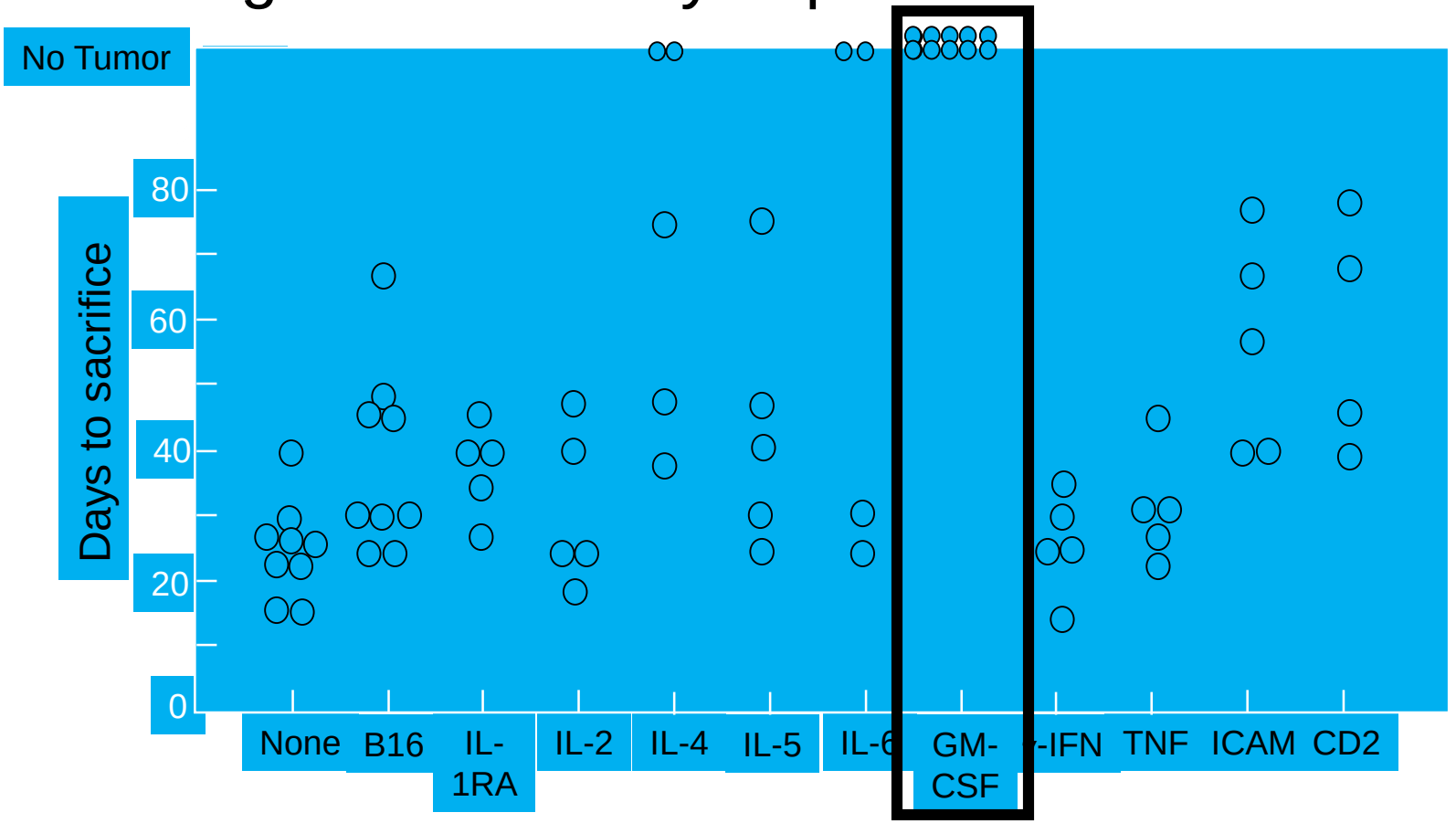
Adapted from Soares, Expert Opin Biol Ther. 2010 May;10(5):841-51.

Tumor cell vaccines: GVAX



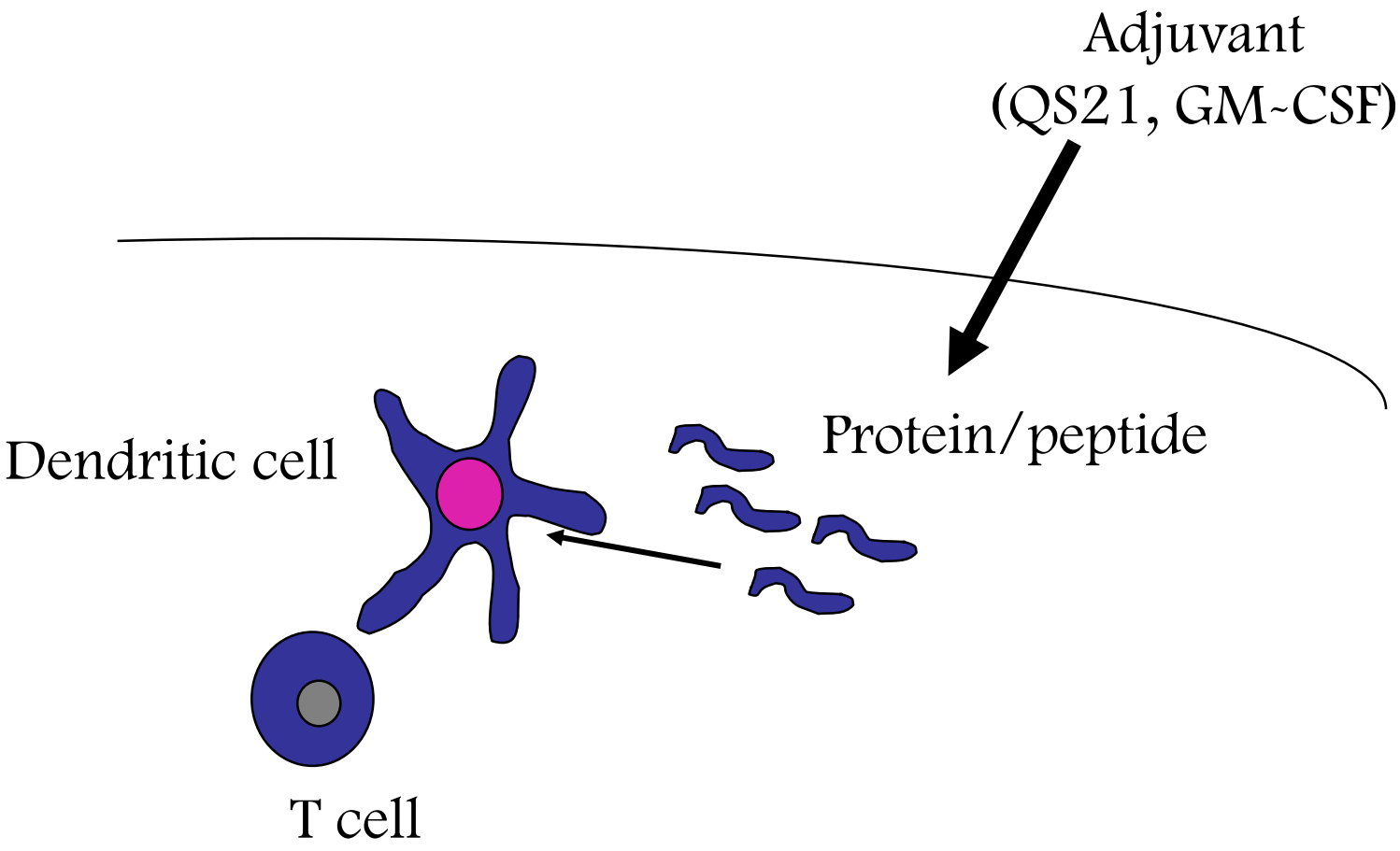
Nature Reviews Urology 10, 149-160 (March 2013)

Tumors Transduced with GM-CSF had greatest activity in preclinical models

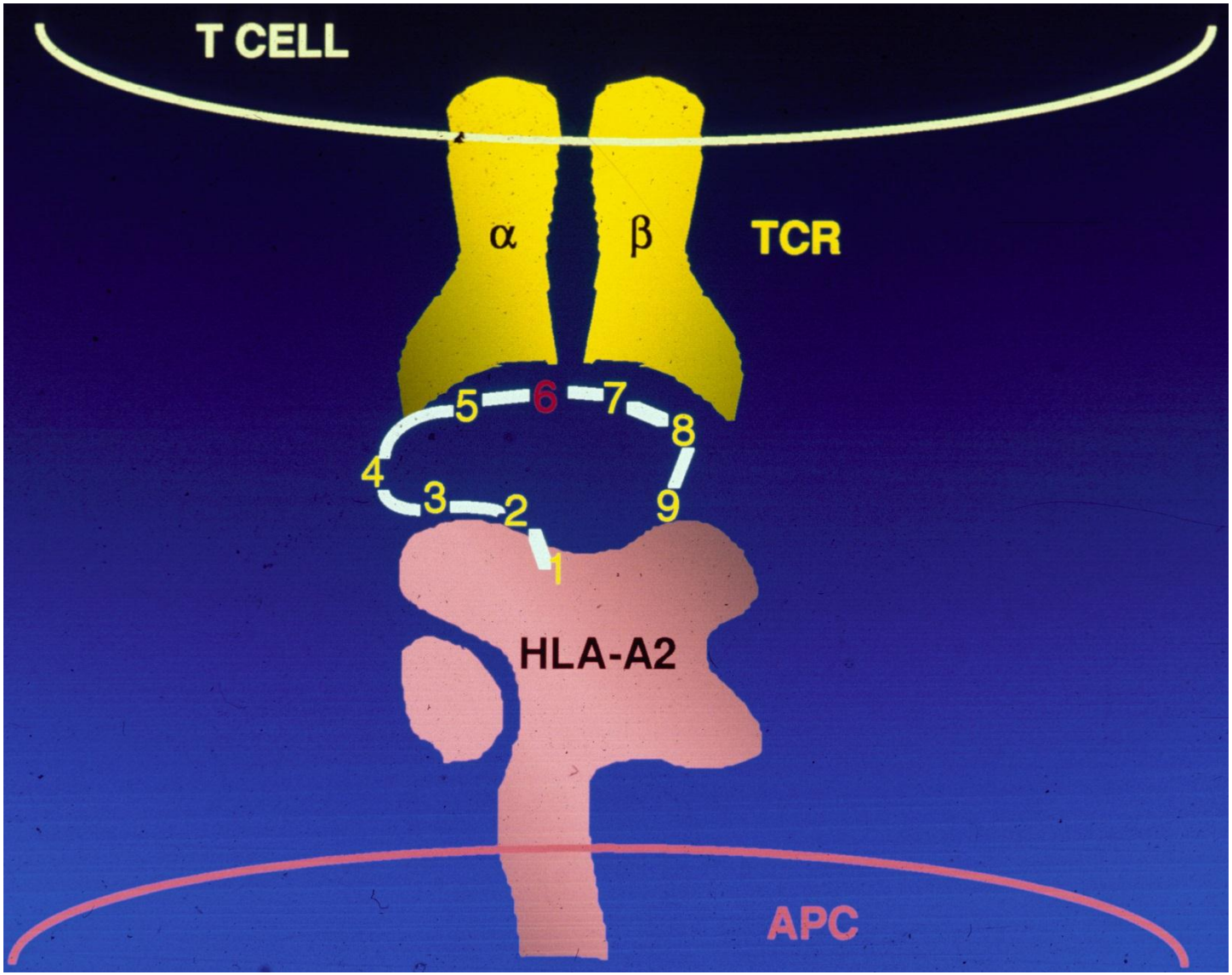


Dranoff G, et al. *Proc Natl Acad Sci USA.* 1993;90:3539-3543.

Peptide & Protein Vaccines



Peptide presented by dendritic cell (APC)



Courtesy: Jeff Schlom, PhD, NCI

Randomized, single-blinded phase II trial of AE37 vaccine versus GM-CSF alone administered in the adjuvant setting to high-risk breast cancer patients (ASCO 2014;#638)

- Disease-free, node+ or high-risk node- pts; any level of HER2 +; completed adjuvant tx
- AE37 + GM-CSF vs GM-CSF alone
- RRR 12 % in ITT group (19/153 v 20/145 events; HR(CI) 0.89 (0.47, 1.66), p=0.70)
- RRR 40% in HER2 nOE pts (10/76 v 14/78 events; HR(CI) 0.60 (0.26, 1.35), p=0.21)
- RRR 60% in TNBC pts (4/25 v 9/25; HR(CI) 0.40 (0.12, 1.32), p=0.12).

Peptide vaccine development

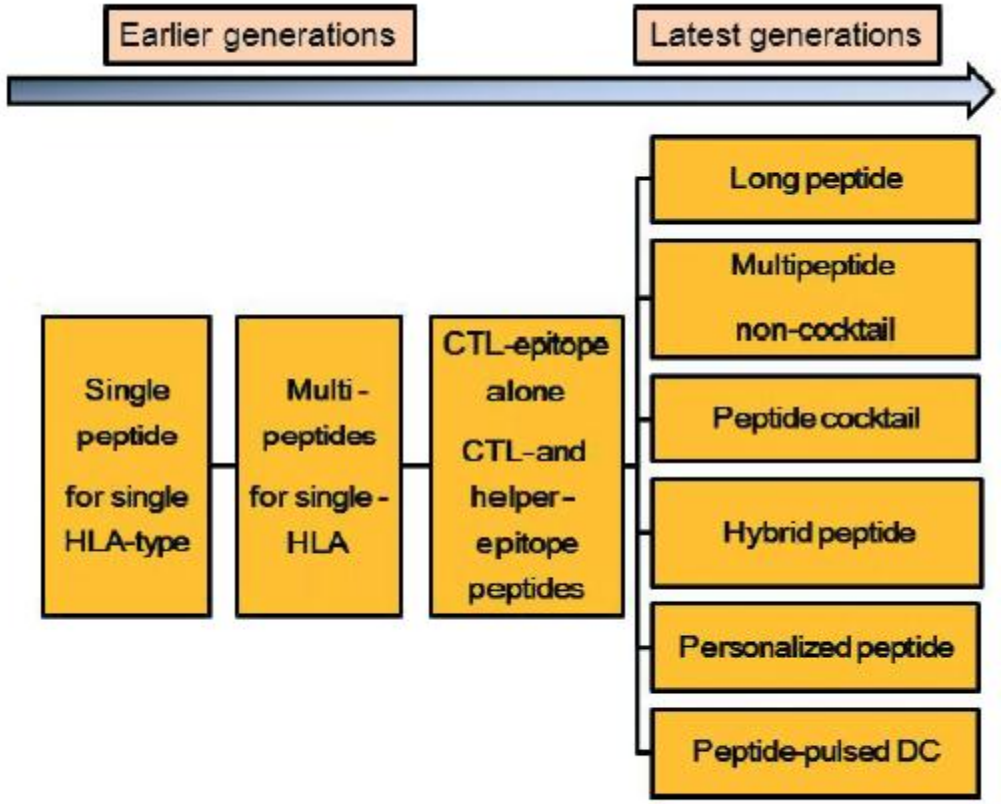
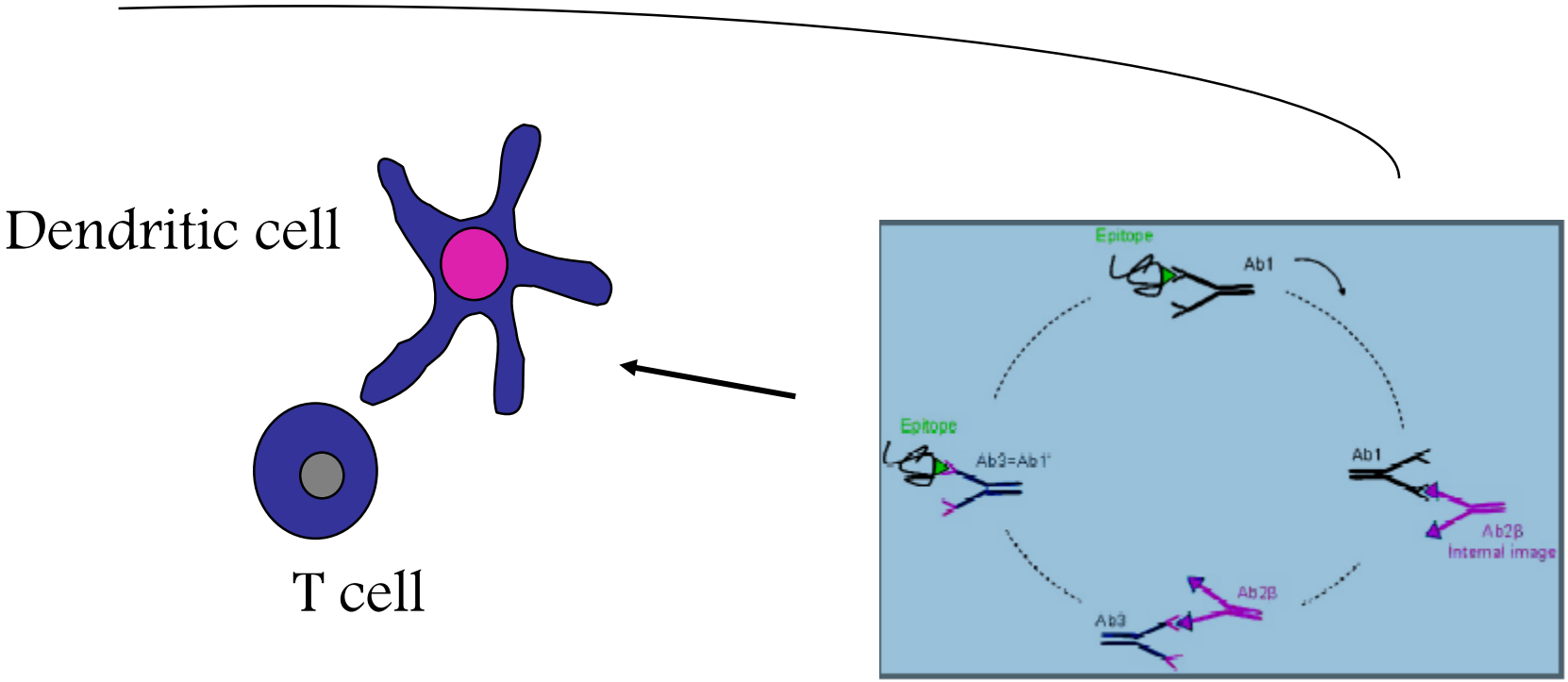


Fig. 1. Transition of peptide vaccine development for advanced cancer. DC, dendritic cells.

Yamada, Cancer Sci 2013;104:15-21

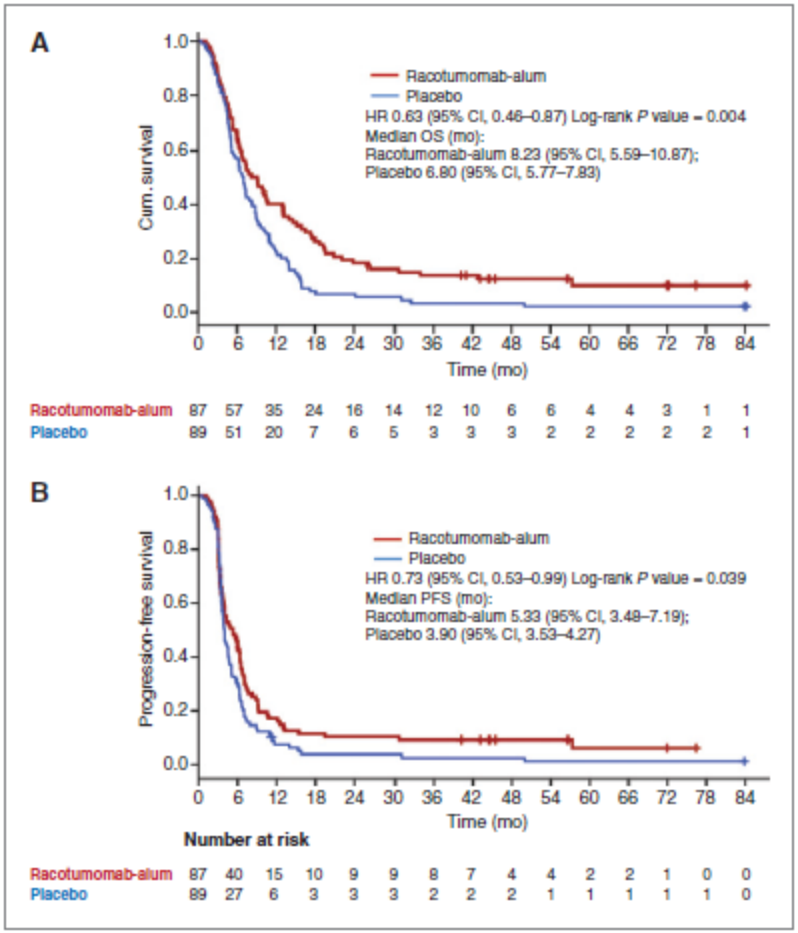
Anti-Idiotype Vaccines: Inducing antibody and T cell responses



Ladjemi MZ. Front Oncol. 2012 Nov 6;2:158.

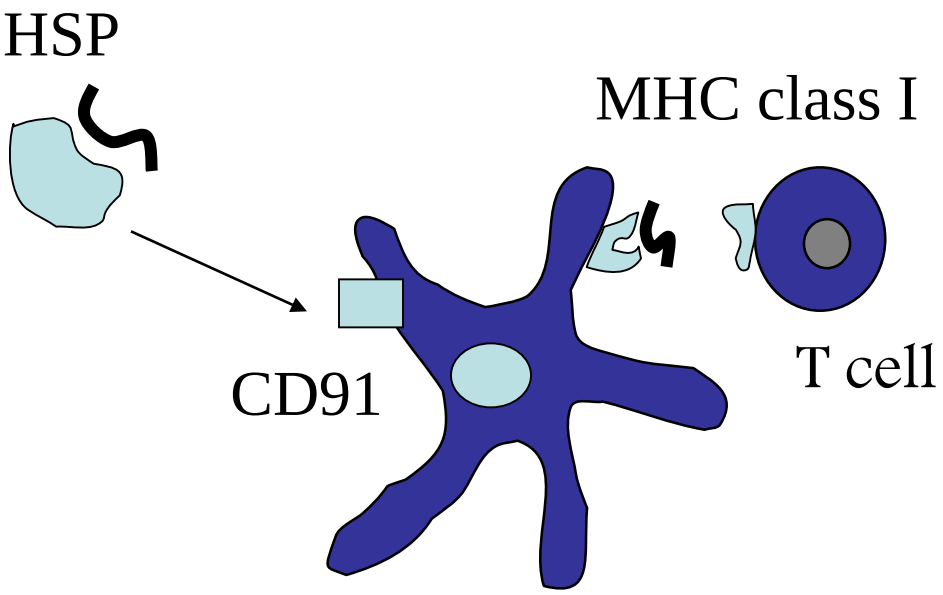
Racotumomab-alum: an anti-idiotype vaccine targeting the NeuGcGM3 tumor-associated ganglioside

A Randomized, Multicenter, Placebo-Controlled Clinical Trial of Racotumomab-Alum Vaccine as Switch Maintenance Therapy in Advanced Non–Small Cell Lung Cancer Patients



Alfonso, Clin Cancer Res. 2014 Jul 15;20(14):3660-71

Heat Shock Proteins



HSP are chaperone proteins

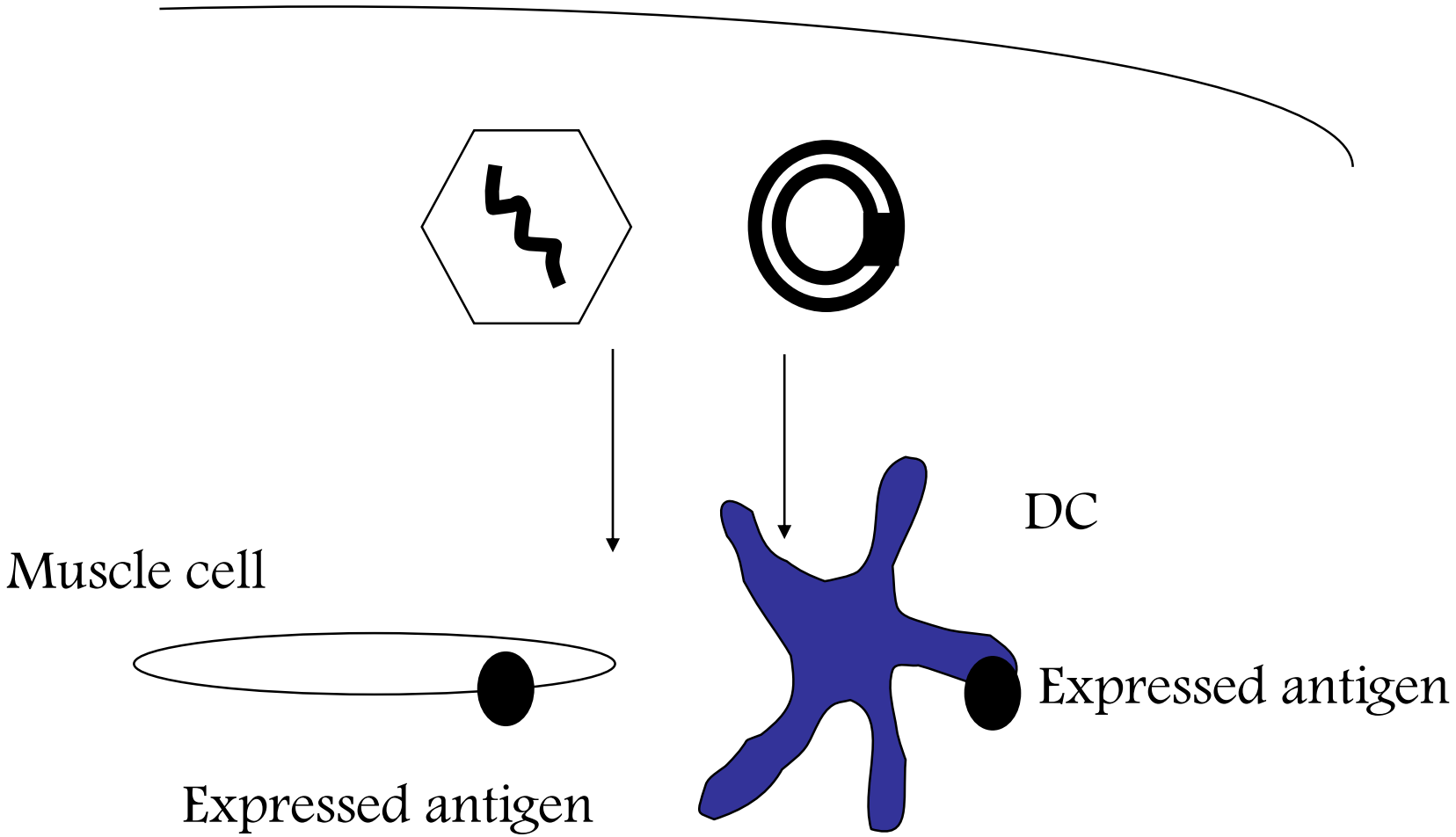
Preps. of HSP (gp96, HSP-70, HSP 90 are noncovalent complex of HSP + peptides

Peptides include normal self and antigenic peptides

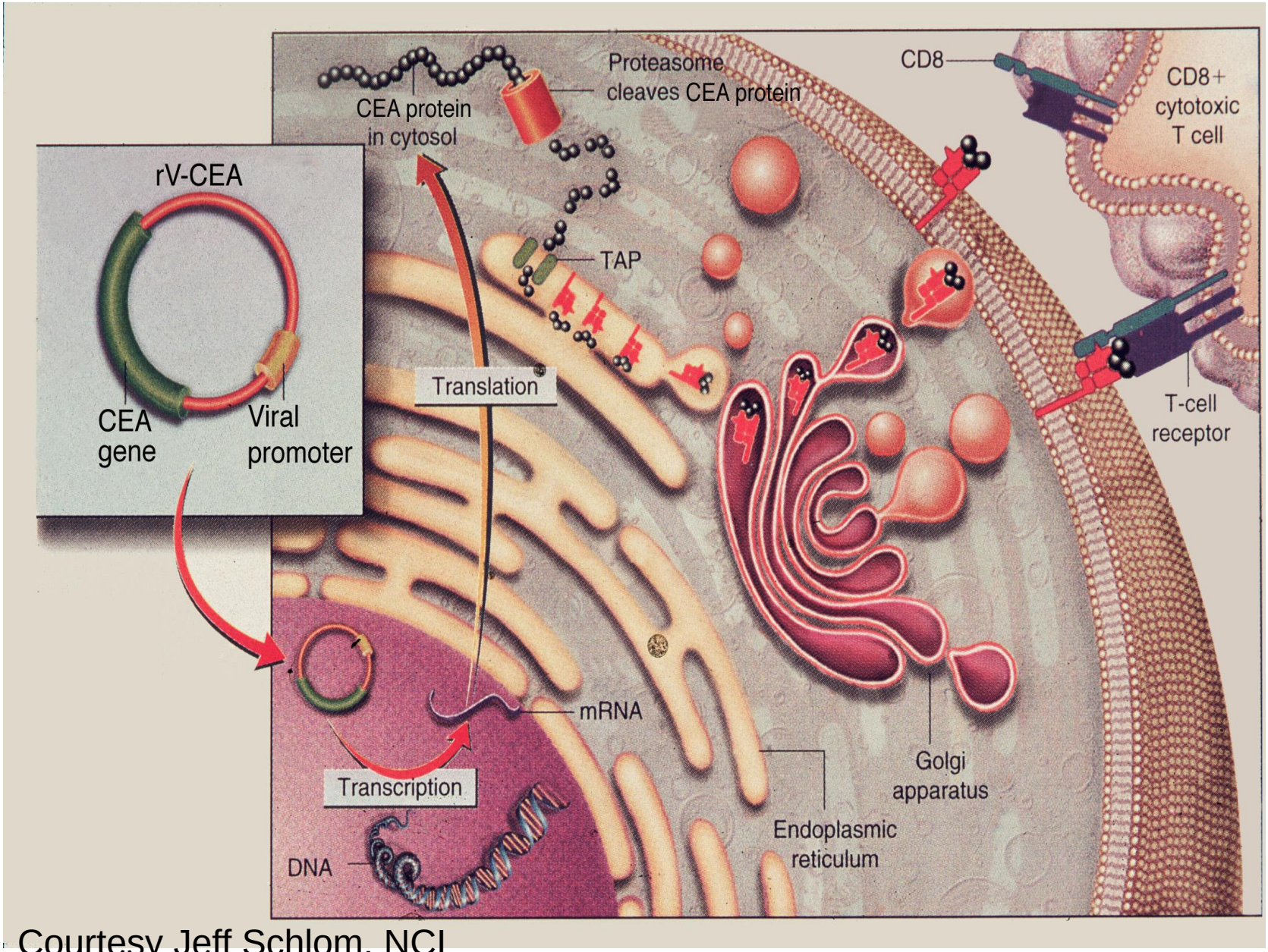
HSP bind to CD91 of APCs such as DC and peptide is processed and presented to T cells by MHC class I

Immune resp is individually tumor-specific (i.e. against non-shared Ag)

Viral Vector & Plasmid Vaccines



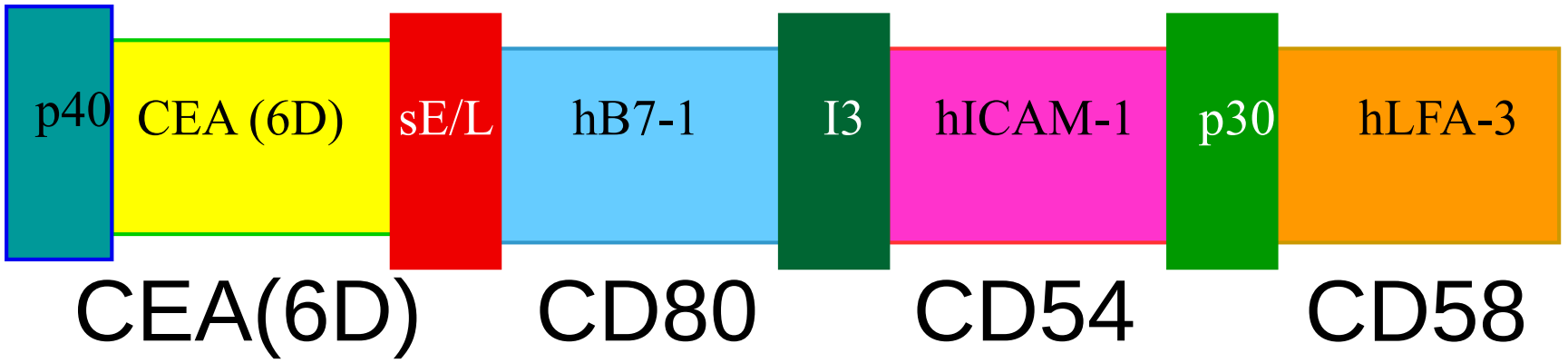
Viral vector based vaccines



Courtesy Jeff Schlom, NCI

Fowlpox vector (rF-CEA(6D)-TRICOM) vaccine

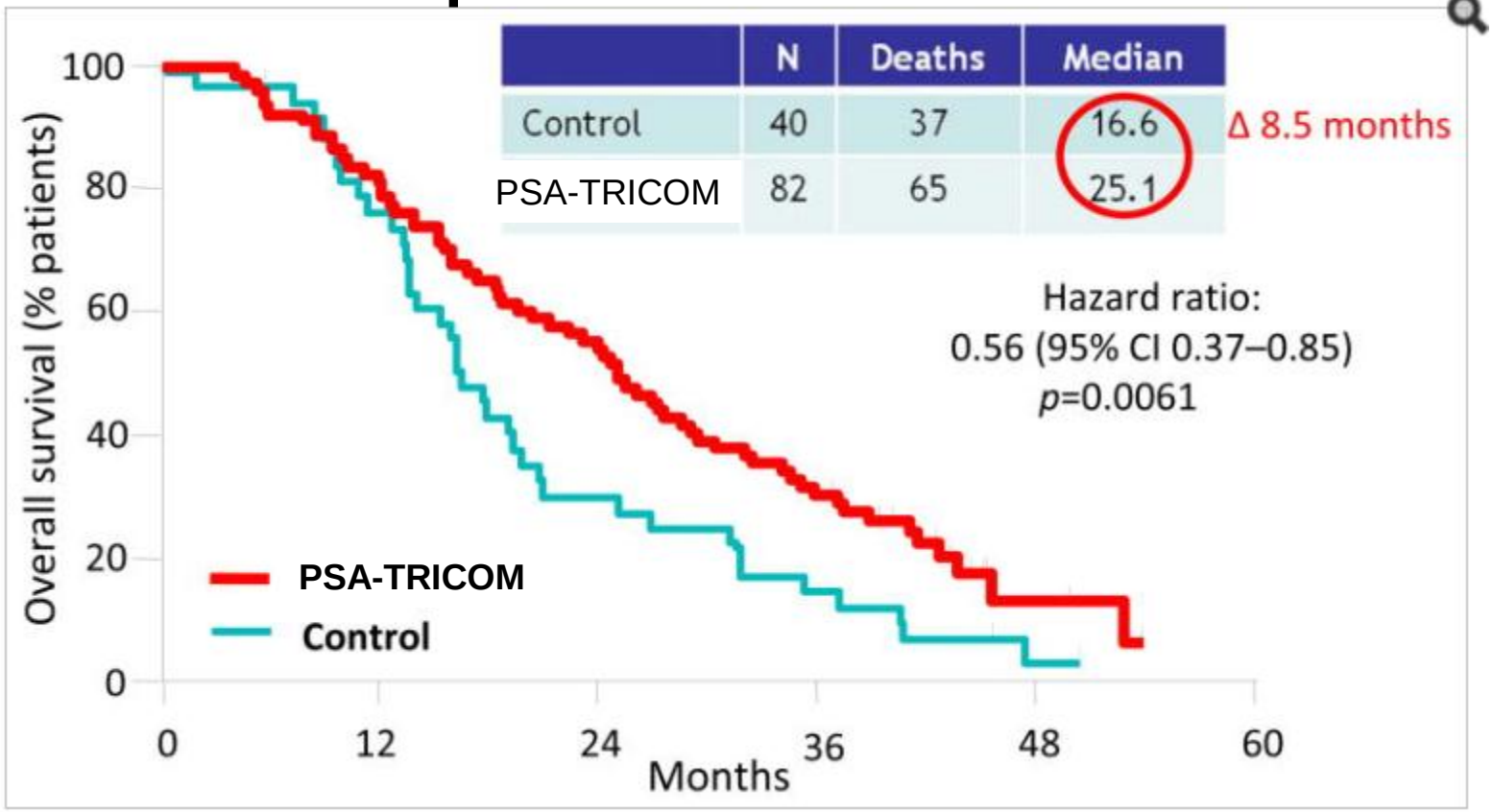
- Fowlpox infect human cells but cannot replicate
- Do not integrate into the host DNA
- Large capacity; express multiple genes
- Induce minimal anti-vector immune response
- Activate CEA(+) T cells (Marshall, ASCO 2003)



Viral Vector	Advantages	Disadvantages
Mammalian Poxviruses • Vaccinia Virus (VV) • Modified virus Ankara (MVA)	• Easily manipulated in laboratory setting • Accepts large gene inserts • Naturally immunogenic • Cellular and humoral immune response to transgene • Expresses transgenes in target cells, including DC • No risk of insertional mutagenesis • MVA strain is replication-incompetent	• Neutralizing antibodies develop with subsequent vaccinations; recipients of vaccinia (smallpox) vaccine have pre-existing immunity to vector • Replication-competent virus (VV), not appropriate for use in immunocompromised patients
Avian Poxvirus • Fowlpox • Canarypox (ALVAC)	• Incomplete lifecycle in mammalian cells, no infectious viral particles can form • Multiple vaccinations possible, no neutralizing antibodies develop	• Immune response is not as robust as vaccinia virus
Adenovirus (Ad)	• Easily manipulated in laboratory setting • Cellular and humoral immune response to transgene • High expression of transgene • Broad tropism, including DC • No risk of insertional mutagenesis • Many strains available • Replication-deficient strains used, limiting pathogenicity	• Infection of target cells dependant on express of Ad receptor (e.g. CAR), which is not expressed on all cancer cells • Pre-existing host neutralizing antibodies to several Ad serotypes • Limited capacity for gene inserts
Alphavirus	• Naturally immunogenic • High expression of transgene • Replicon-competent vector • No neutralizing antibodies develop against non- propagating vector • Broad tropism • Multiple vaccinations possible, no neutralizing antibodies develop	• Limited capacity for gene inserts • Limited duration of expression of transgene due to induction of apoptosis in infected target cell

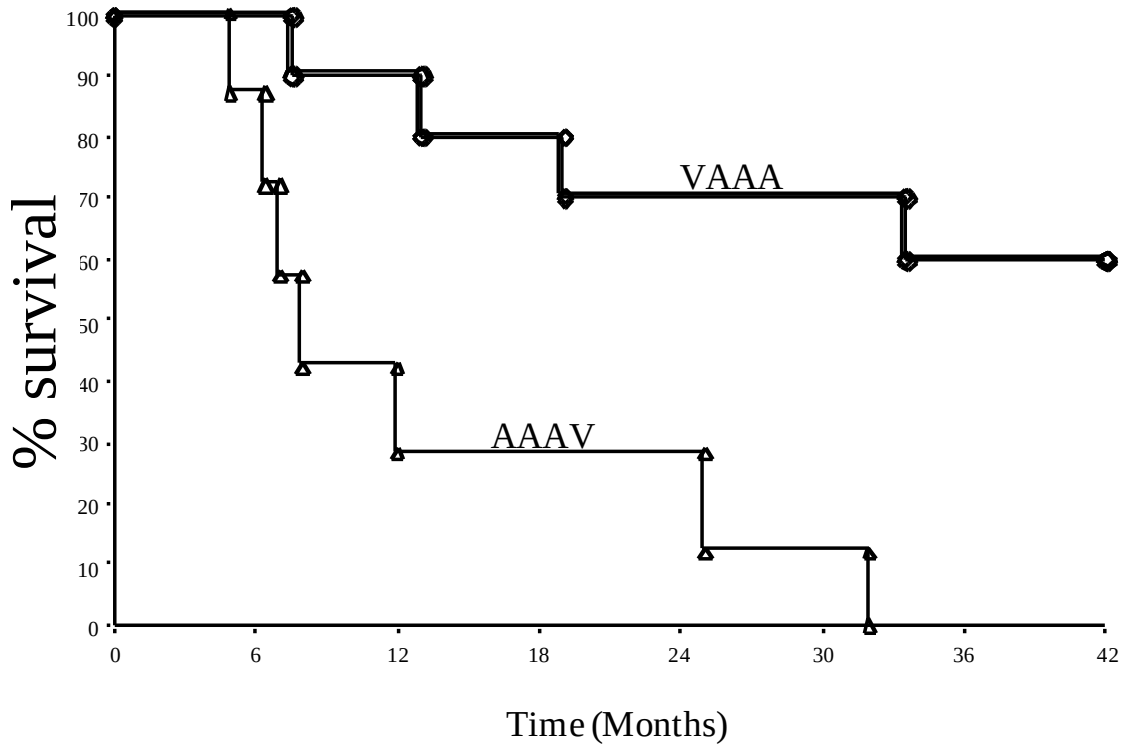
LaRocca, Cancer J. 2011 Sep-Oct;17(5):359-71.

Randomized trial of PSA-TRICOM in prostate cancer

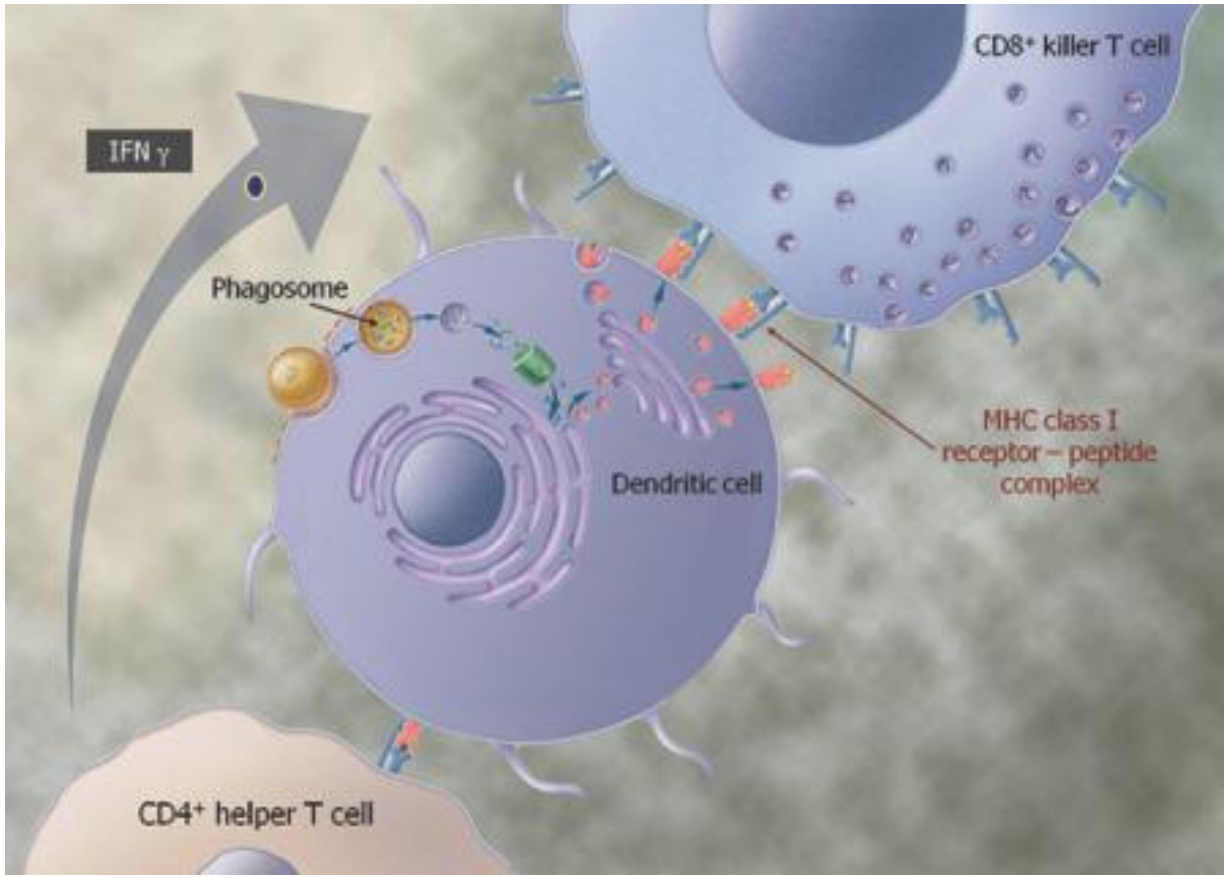


Schlom, Adapted from Kantoff P, J Clin Oncol. 2010;28:1099–1105.

Prime-boost with poxvectors is clinically active



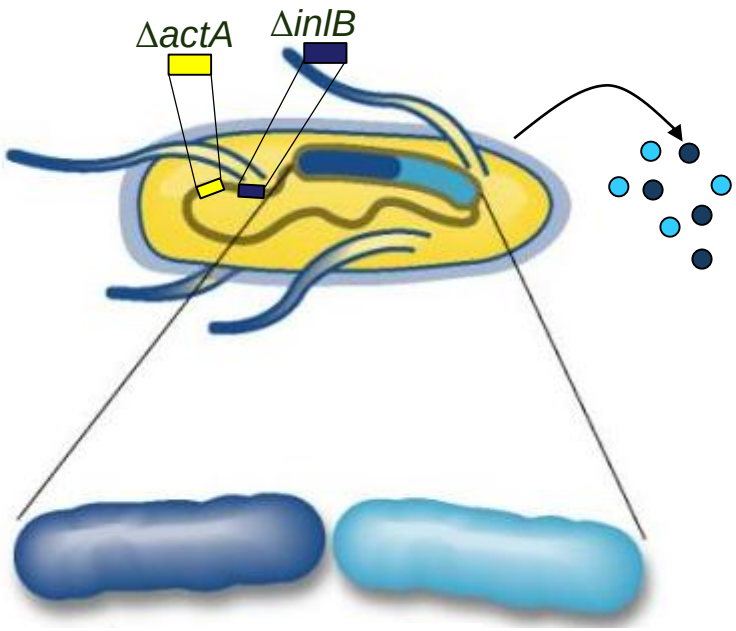
Yeast vectors



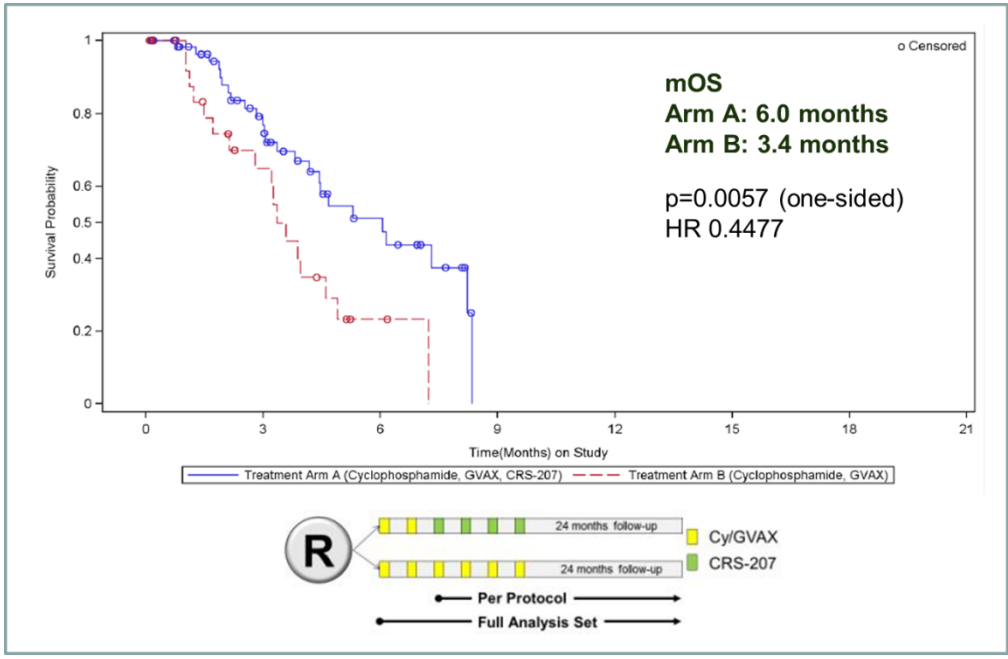
Bacterial vector: CRS-207 (Listeria-mesothelin)

LADD Listeria
Live-attenuated *Listeria monocytogenes*

- Potent activation of innate and antigen-specific immune response



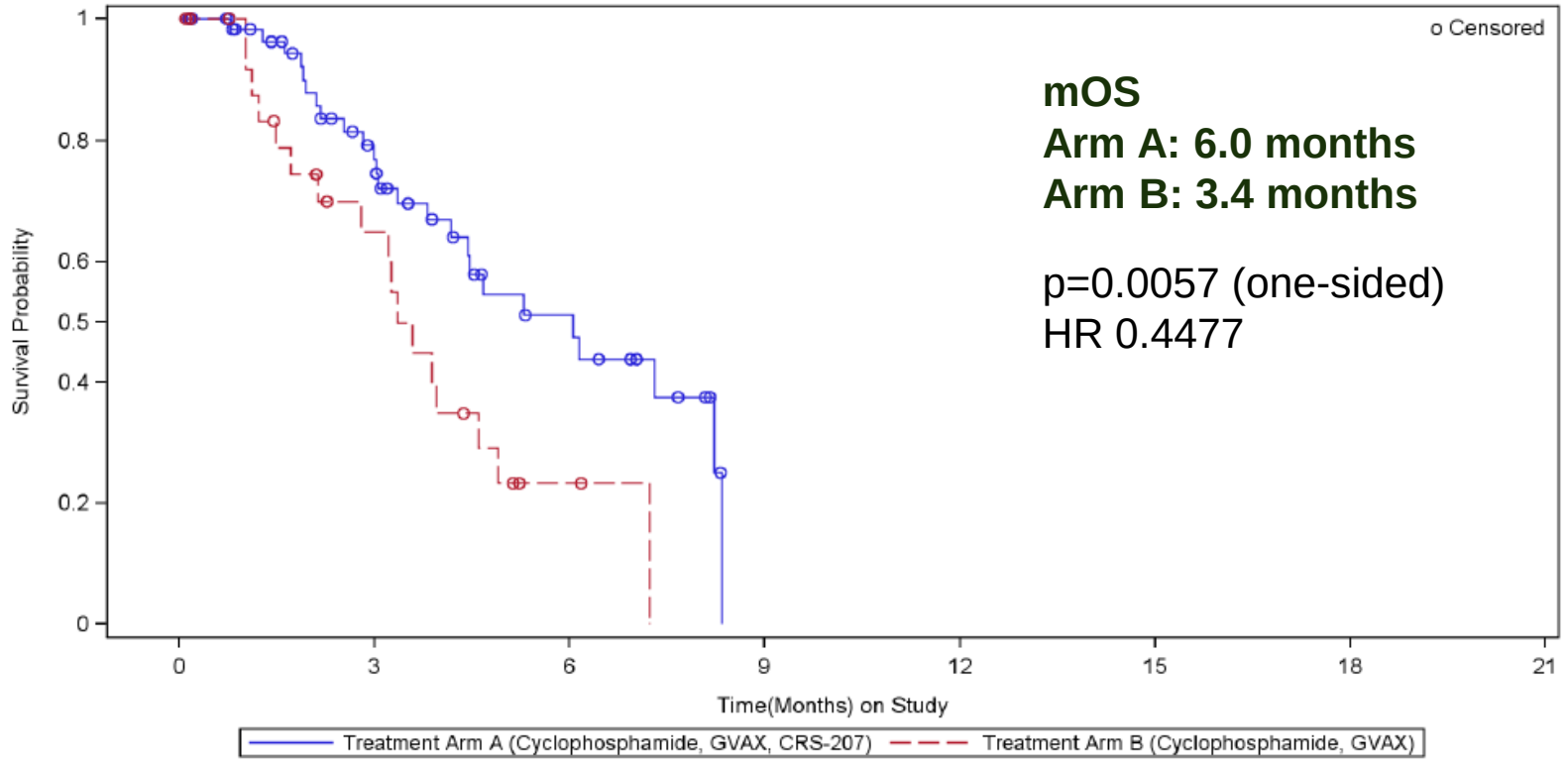
Mesothelin



Le D, GI ASCO 2014

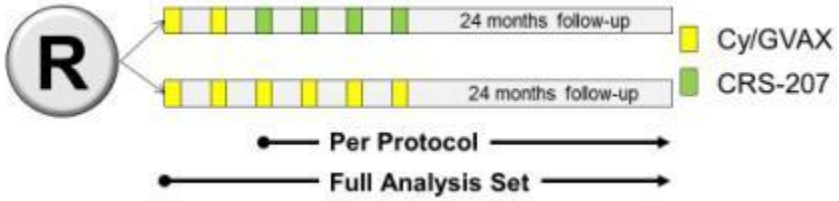
Overall Survival – Full Analysis Set

(Planned Interim Analysis, Jan 2013)

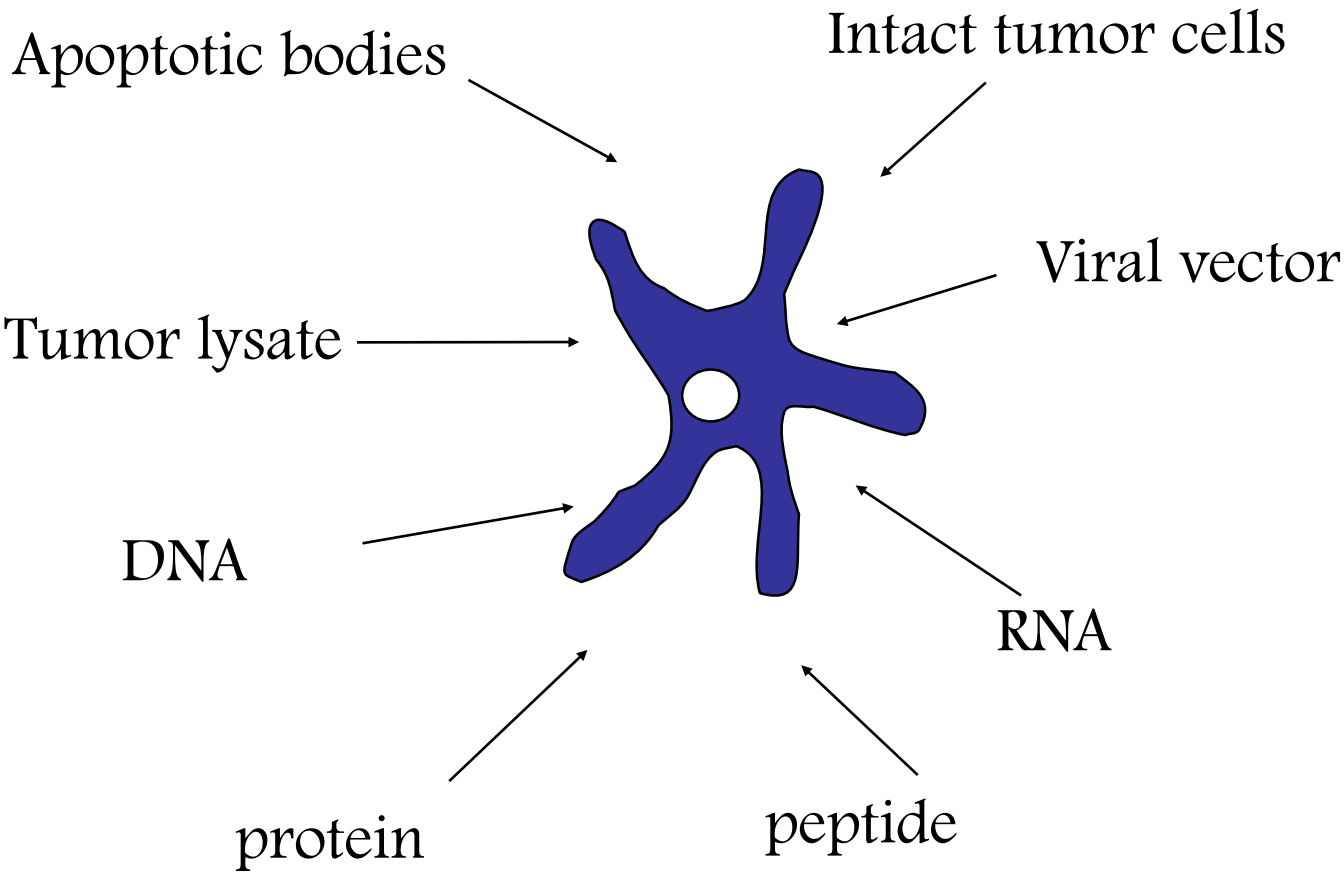


mOS
Arm A: 6.0 months
Arm B: 3.4 months

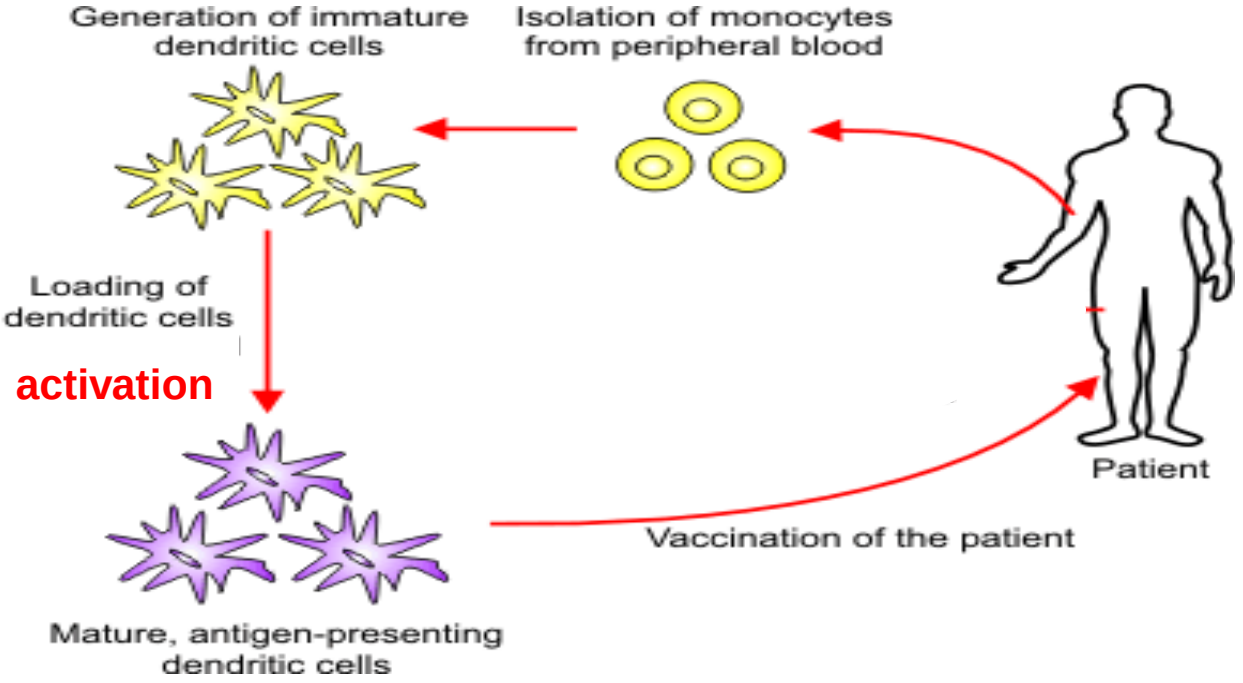
p=0.0057 (one-sided)
HR 0.4477

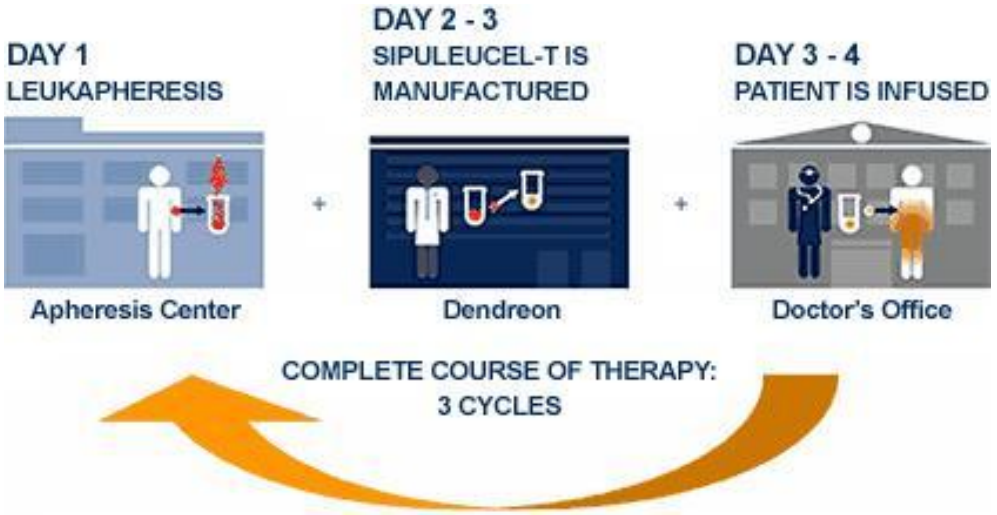


Dendritic cell vaccines



Autologous antigen presenting cell for cancer immunotherapy





Dendritic cell vaccine: Sipuleucel-T

Phase III RCT of APC8015 for androgen-independent prostate Ca (***J Clin Oncol 2006;24:3089-3094***)

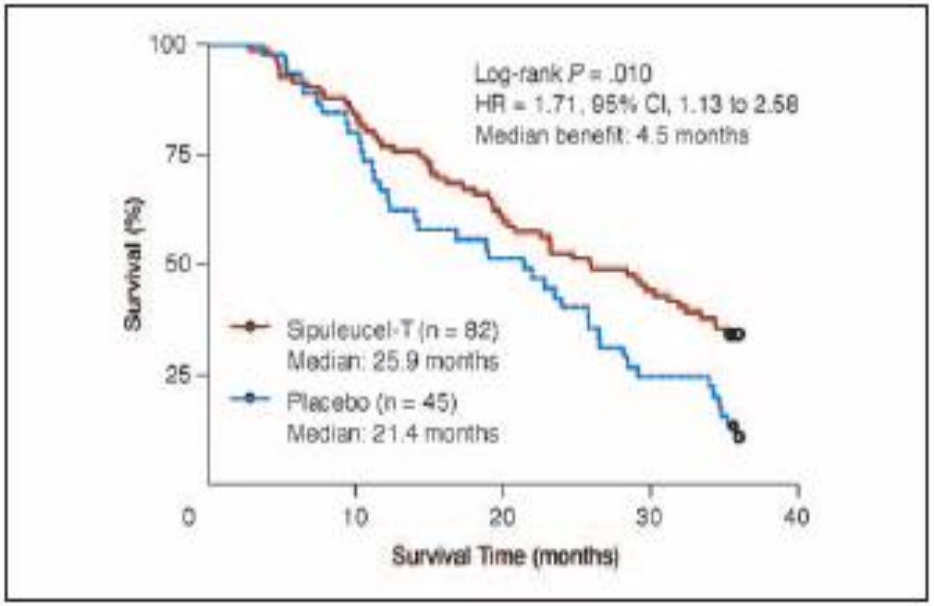


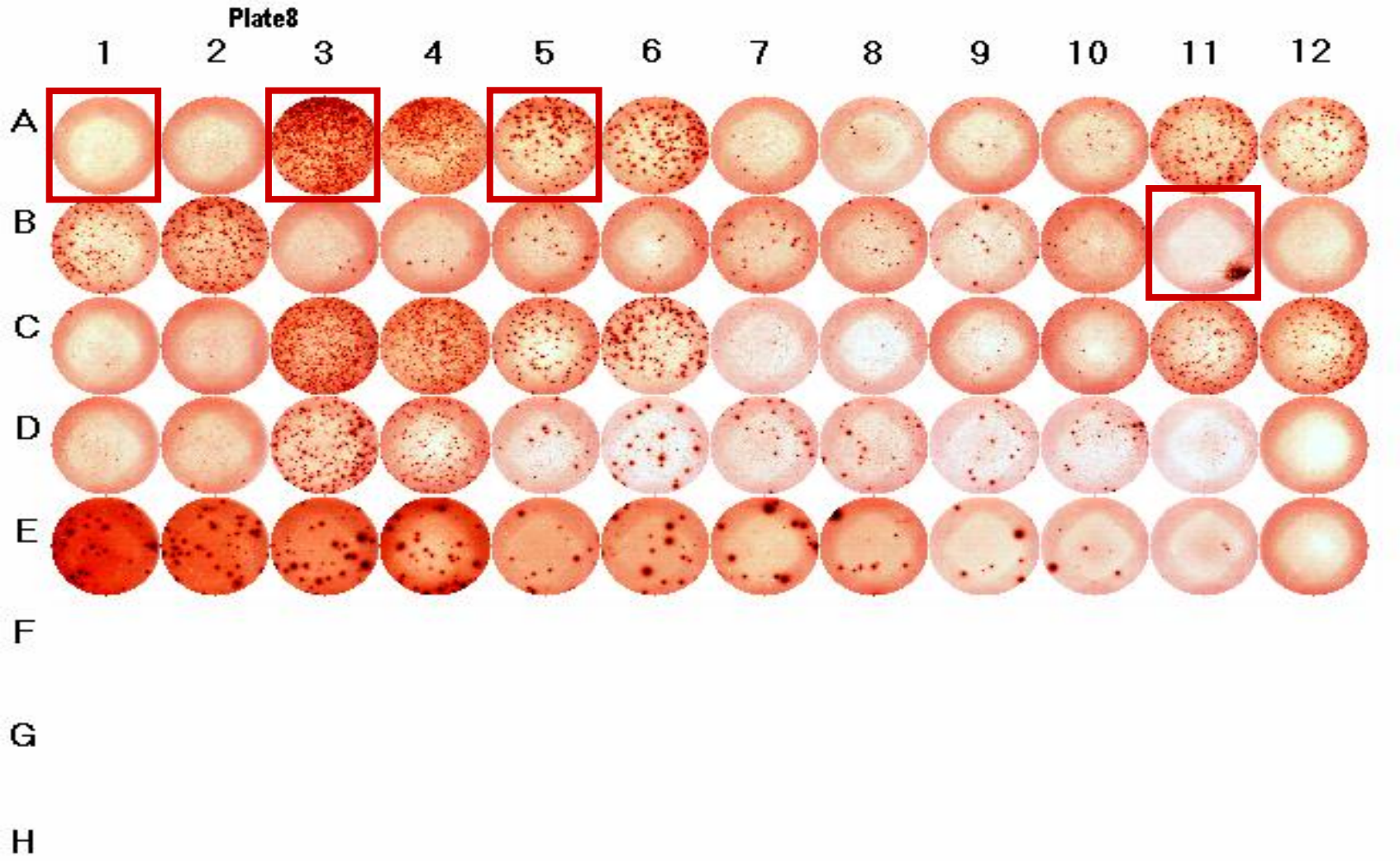
Fig 3. Final overall survival (intent-to-treat population). HR, hazard ratio.

Most common AE: chills (in 51.2%), fever (22.5%), fatigue (16.0%), nausea (14.2%), headache (10.7%).

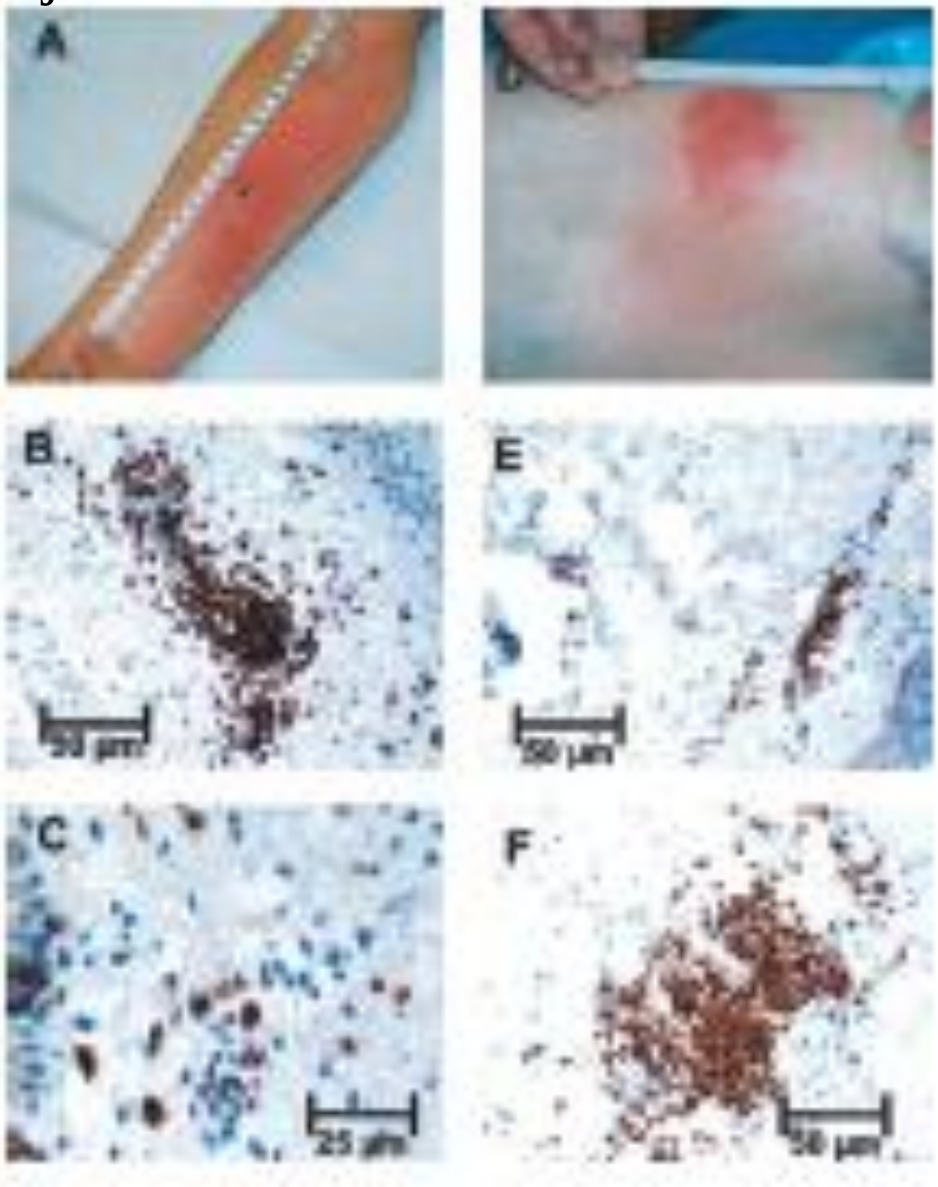
OS significantly improved

MEASURING IMMUNE RESPONSES TO VACCINES

Detecting immune response by ELISPOT After Vaccination



Measures of immune response to vaccines
Injection site and DTH reactions



JNCI 2004;96:326

Immune response Correlates with

OS

DFS

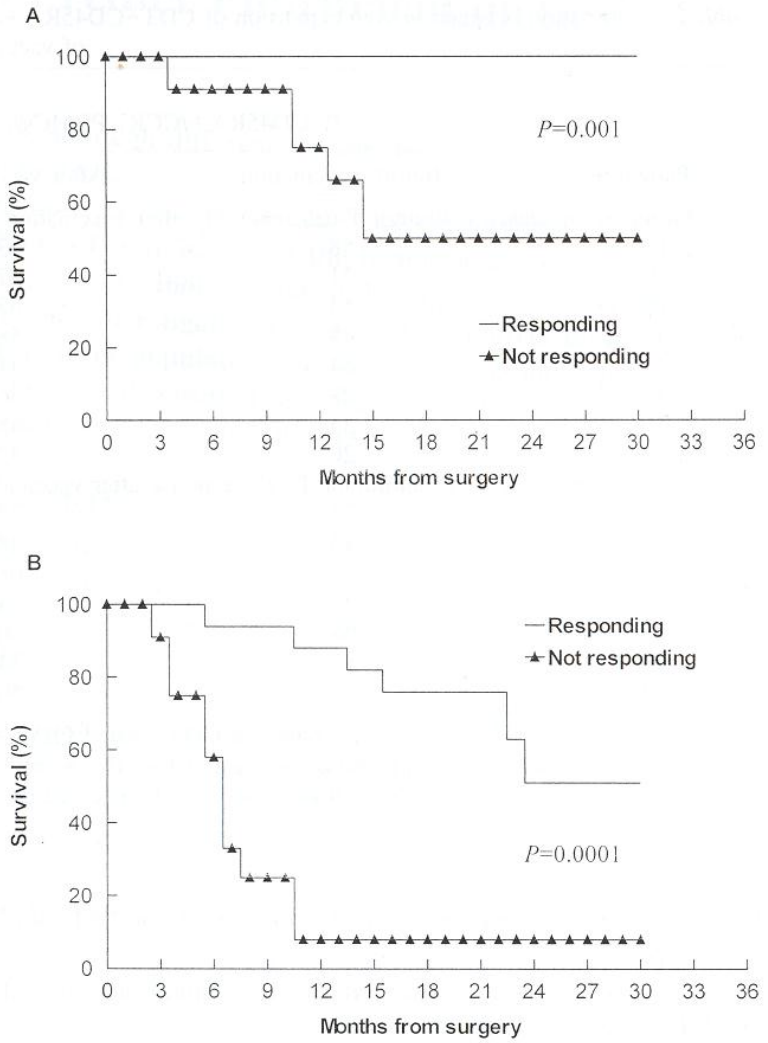
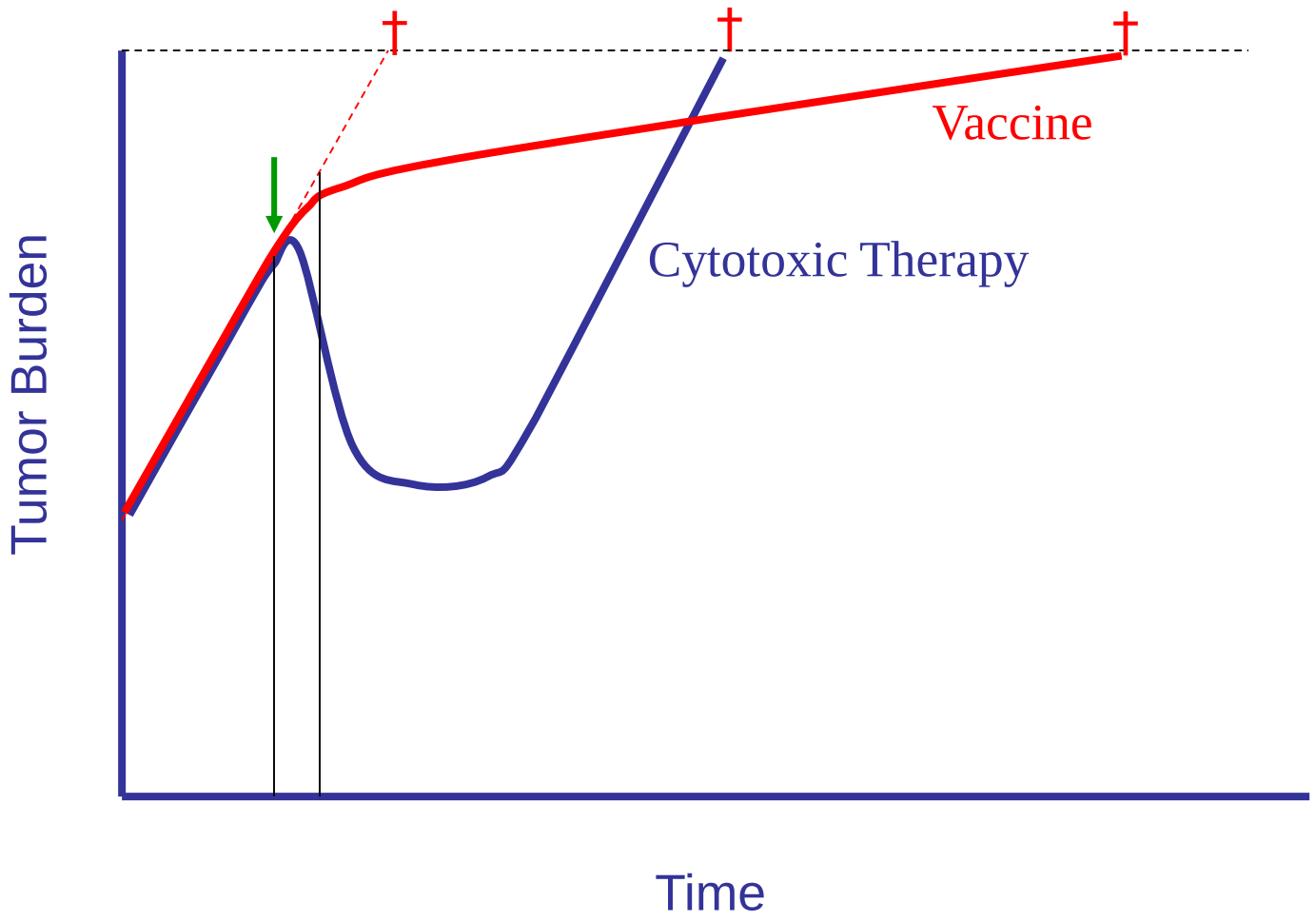


Fig. 4 Different clinical outcome between immune responders and nonresponders vaccinated with HSPPC-96 after complete liver resection of metastatic CRC. Patients with a postvaccination immune response (17 cases) had a significant survival advantage at 24 months compared with that of nonresponding patients (12 cases) both on OS (*A*; 100 *versus* 50% at 2 years) and on DFS (*B*; 51 *versus* 8% at 2 years).

Clin Ca Res 9:3235, 2003

Tumor Growth Rate



Stein W, Gulley JL, et al. *Clin Ca Res*, 2011

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- A. Cross presentation of antigen by dendritic cells
- B. Antigen unique to tumor
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Antigens used in vaccines are often normal proteins not unique to tumor, but may be overexpressed or aberrantly expressed

The following statements about viral vector vaccines are true except

- A. Prime-boost vaccination may give stronger immune responses
- B. Viral vectors must directly infect DC to be effective
- C. Viral vectors may contain multiple genes including those to provide multiple activation signals to T cells

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Due to cross presentation, viral vectors can infect other tissues and still induce immune responses