NASDC
NCI Awardee Skills Development Consortium

Cancer Vaccines and Locoregional Immunotherapies

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Disclosures

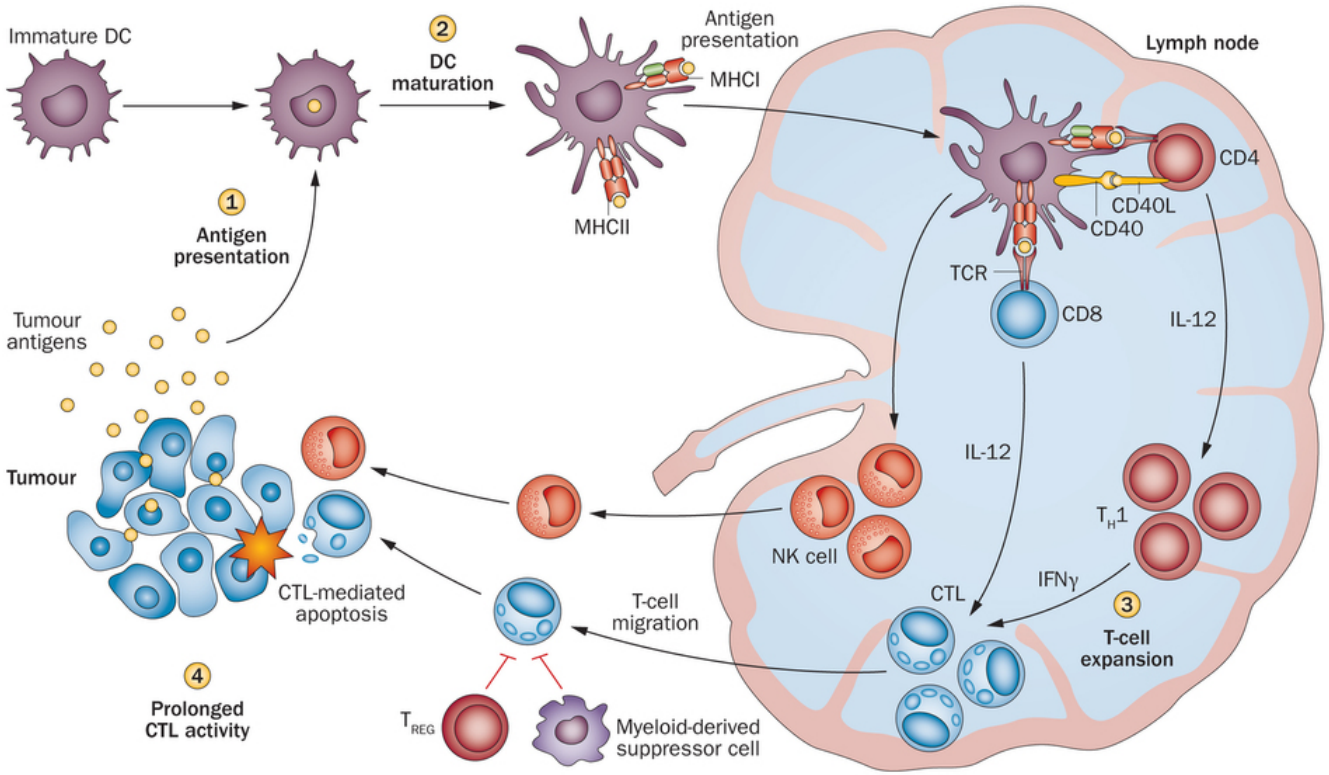
Research support:

» Merck, Roche/Genentech, Kyowa, Turnstone Biologics, Astra Zeneca, Plexxikon

Consulting

» Biomed Valley Discoveries, Synlogic Therapeutics, Hookipa Biotech, Tesaro, Western Oncolytics, Roche, Xencor, Targovax

Steps in development of anti-tumor immune response



Melero et. al, Nature Reviews Clinical Oncology, 2014

Breaking immune tolerance: how does the immune system recognize the tumor as non-self?

- B and T lymphocytes that react against self-proteins are eliminated during development
- Self-reactive lymphocytes presented with self-antigens are rendered anergic
- Persistence or development of self-reactive lymphocytes causes autoimmune diseases
- **The major challenge of tumor vaccines is to break the immune tolerance to tumor-antigens**

Source: pinterest.com

Recognition of cancer by the adaptive immune system is dependent on tumor antigens

Tumor-associated antigens (TAA): expressed primarily in tumor, but may also be expressed in normal tissues

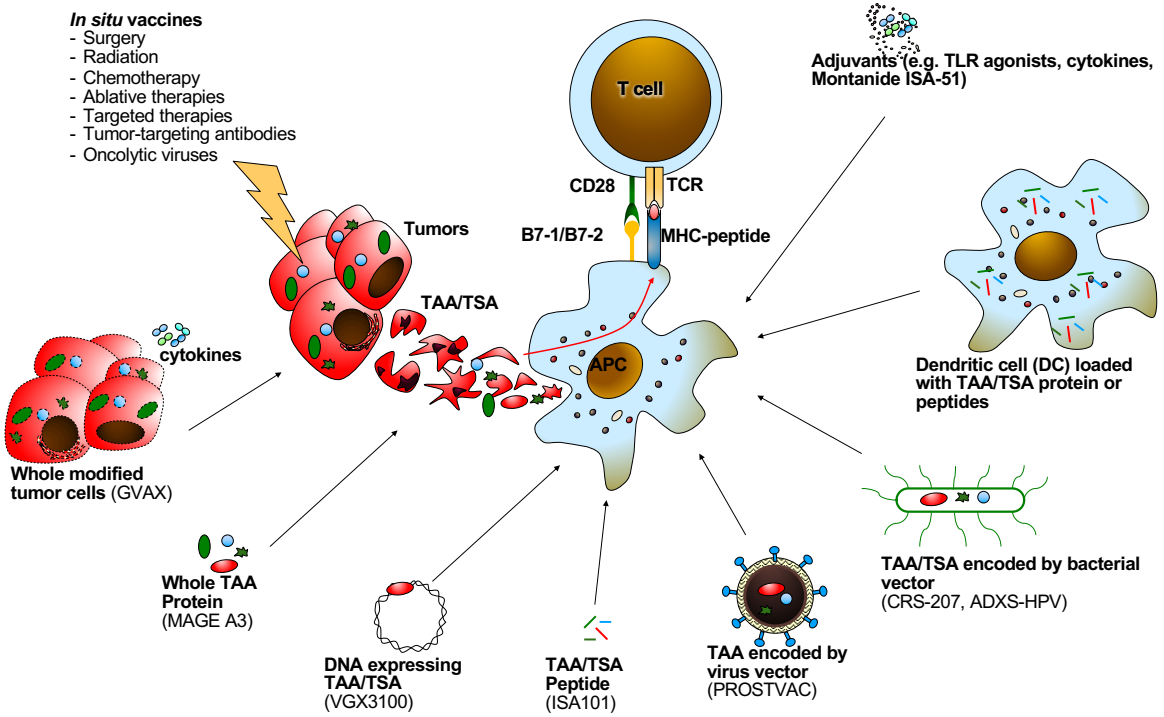
- **Tissue-specific antigens:** non-mutated self-proteins more prevalent on cancer cells (e.g. gp100, CD20, Her2/neu, CEA, PSA, mesothelin).
- **Oncofetal (differentiation) antigens:** proteins expressed during development, but not in adult life (e.g. AFP)
- **Cancer-Germline Antigens:** expressed in immune-privileged sites and during development (e.g. NY-ESO1, MAGE A3)
- Glycoproteins with altered side chain carbohydrates (e.g. MUC1).
- Since most TAAs are public, they have an advantage for targeting using off the shelf vaccines
- Due to expression in normal tissues at some point in development, immune system may be tolerant to many TAAs

Recognition of cancer by the adaptive immune system is dependent on tumor antigens

Tumor-specific antigens (TSA): expressed only in tumors

- **Viral antigens in virus-induced tumors** (HPV, EBV)
- Proteins resulting from mutations, insertions/deletions, translocations, and alternative processing: also known as neoantigens
- Most TSAs are private and require development of personalized vaccines; however, neoantigens resulting from recurrent molecular alterations (e.g. hotspot mutations) and viral antigens can be used for development of off the shelf vaccines

Cancer vaccines aim to enhance recognition of tumor antigens by the immune system (by boosting pre-existing responses or development of new responses)



Vaccine adjuvants

Adjuvants stimulate the immune system's response to the target antigen, but do not in themselves confer immunity

Types:

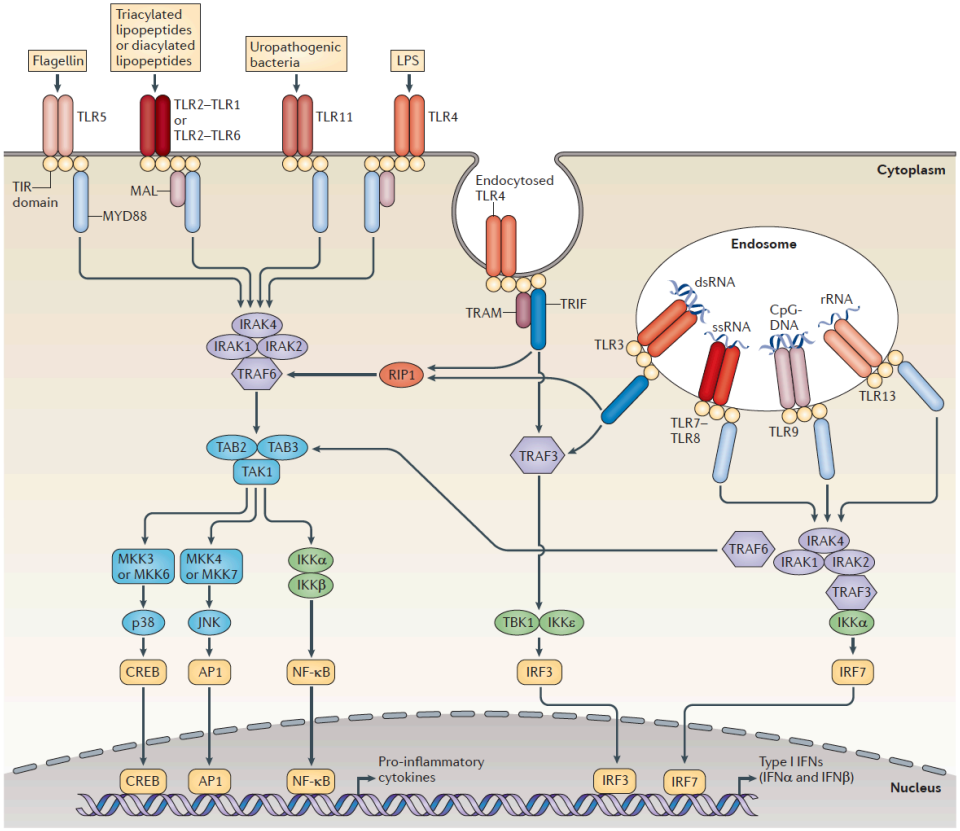
- Inorganic compounds (aluminum hydroxide, aluminum phosphate, beryllium)
- Mineral oil (paraffin oil)
- Bacterial products (killed bacteria, Mycobacterium bovis, toxoids)
- Nonbacterial organics (squalene, thimerosal)
- Detergents (Quil A)
- Cytokines (IL-1, IL-2, IL-12)
- Combinations (complete Freund's adjuvant, incomplete Freund's adjuvant), e.g. Montanide ISA-51

Mechanisms:

- Depots that trap antigens at the injection site providing slow release
- Stabilization of antigen formulation
- Immune stimulation

Many vaccine adjuvants stimulate type I interferon (IFN) response through pattern recognition receptors (PRR)

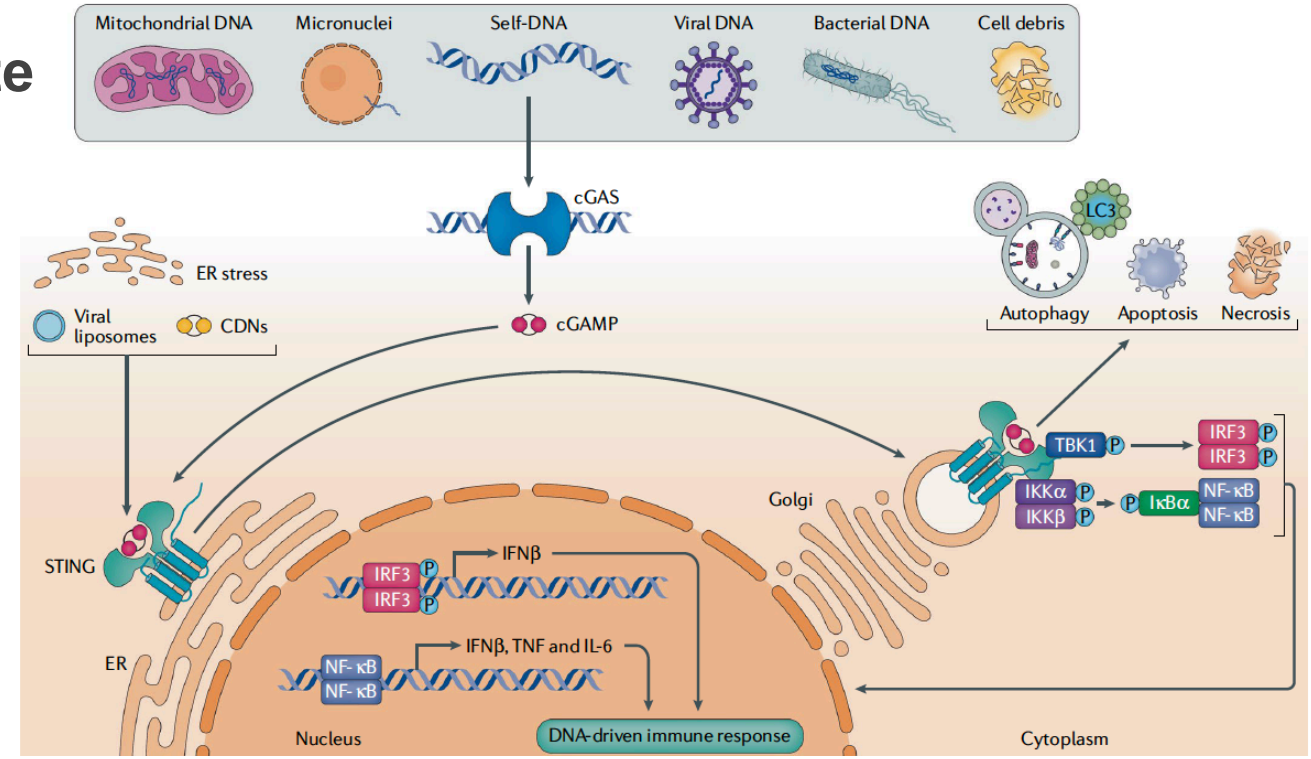
RIG-I-like receptor (RLR) and Toll-like receptors (TLR): activated by pathogen components and nucleic acids



O'Neill et al., Nat. Rev. Immunol 2013

Many vaccine adjuvants stimulate type I interferon (IFN) response through pattern recognition receptors (PRR)

cGAS-STING Pathway: activated by cytosolic DNA



Motwani M. et al., Nat. Rev. Genetics 2019

Activation of innate immune signaling pathways in antigen presenting cells (APCs) plays a key role in vaccine immunity

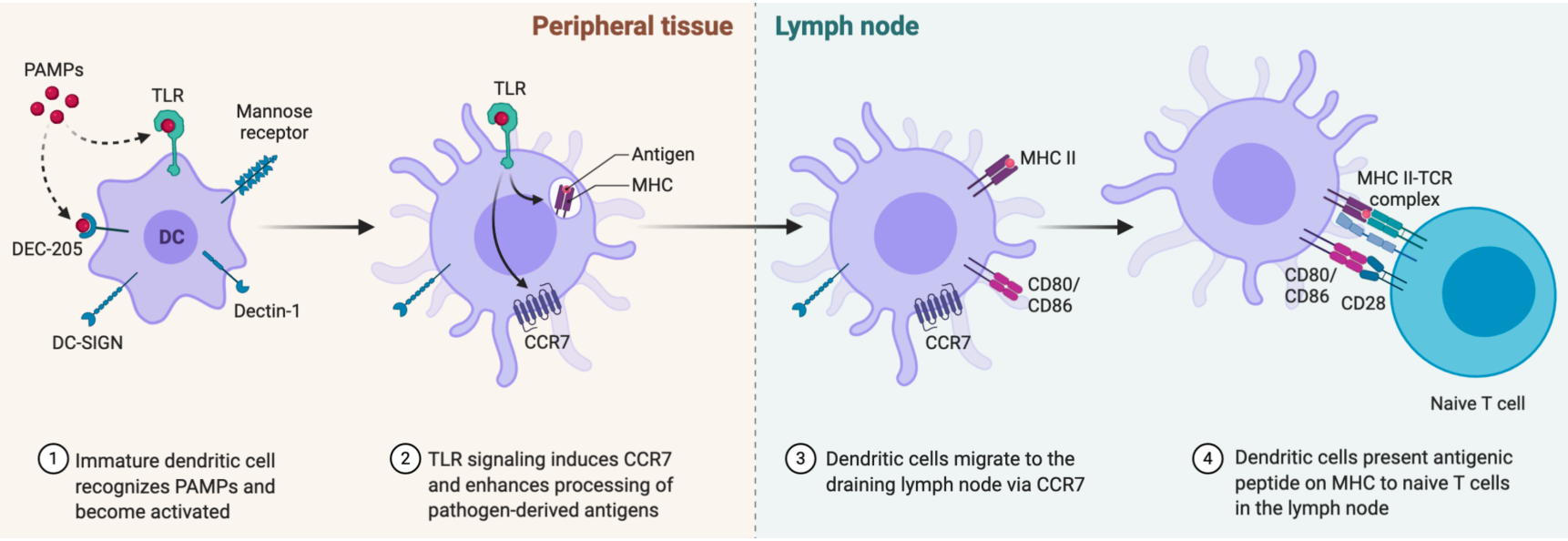
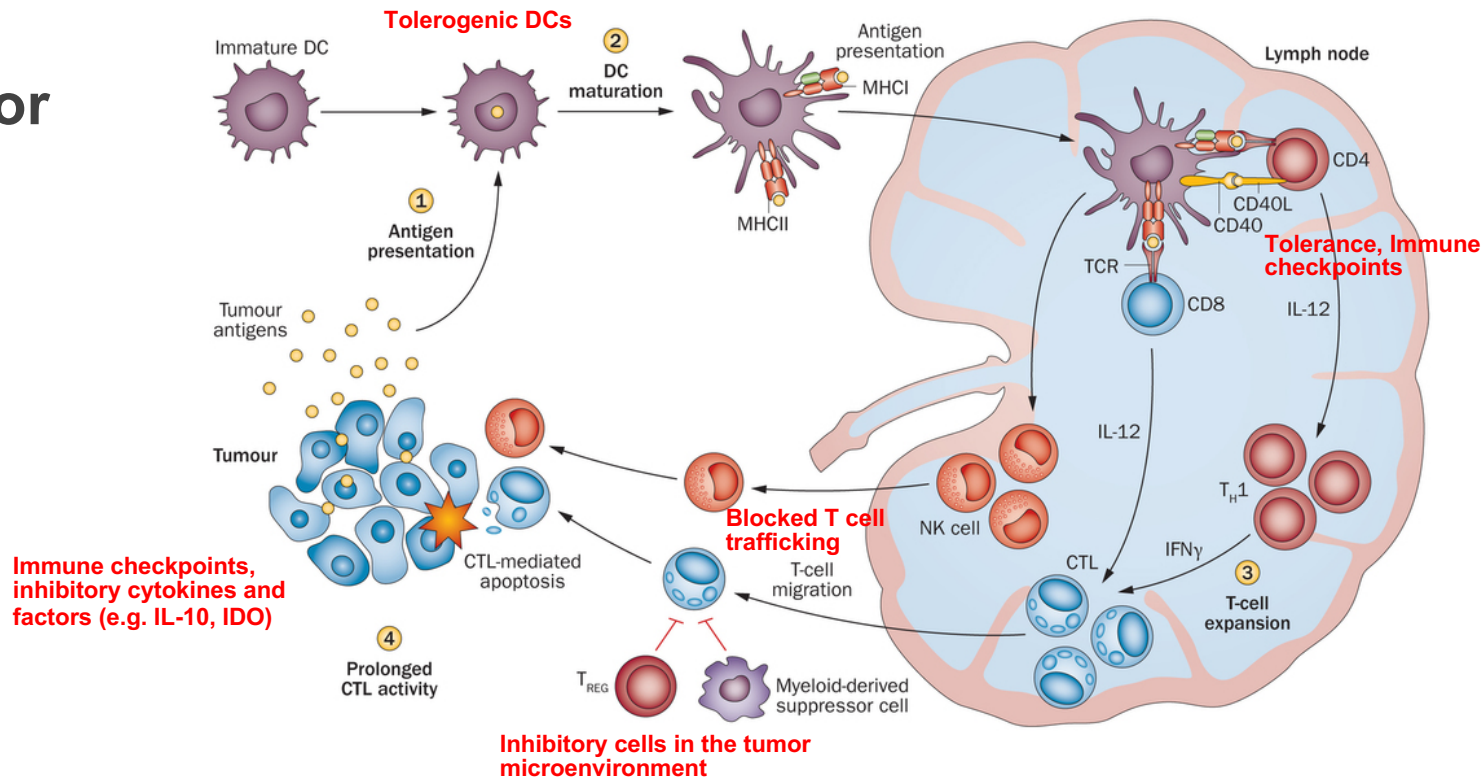


Image created in BioRender

Each step in the anti-tumor immune response presents a barrier to efficacy of vaccines



Adapted from Melero et. al, Nature Reviews Clinical Oncology, 2014

Peptide vaccines

Advantages

- Easy to synthesize
- Require minimal to no processing by APCs

Considerations

- Short vs. long peptides
- Targeting single vs. multiple antigens
- Targeting CD4 vs. CD8 T cell immunity
- Choice of antigen(s)
- Choice of adjuvant
- Early vs. advanced disease setting

Disadvantages

- MHC-restricted
- In general, have marginal therapeutic efficacy as single agents, despite evidence of antigen-specific immune response

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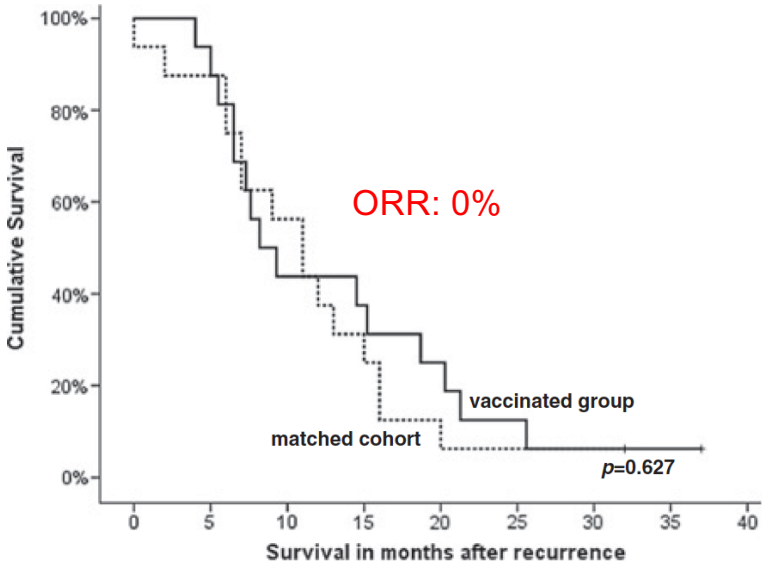
Early disease setting: HPV-16 vaccination for HPV-associated vaginal intraepithelial neoplasia (VIN) 2/3

Kenter et al., NEJM 2009

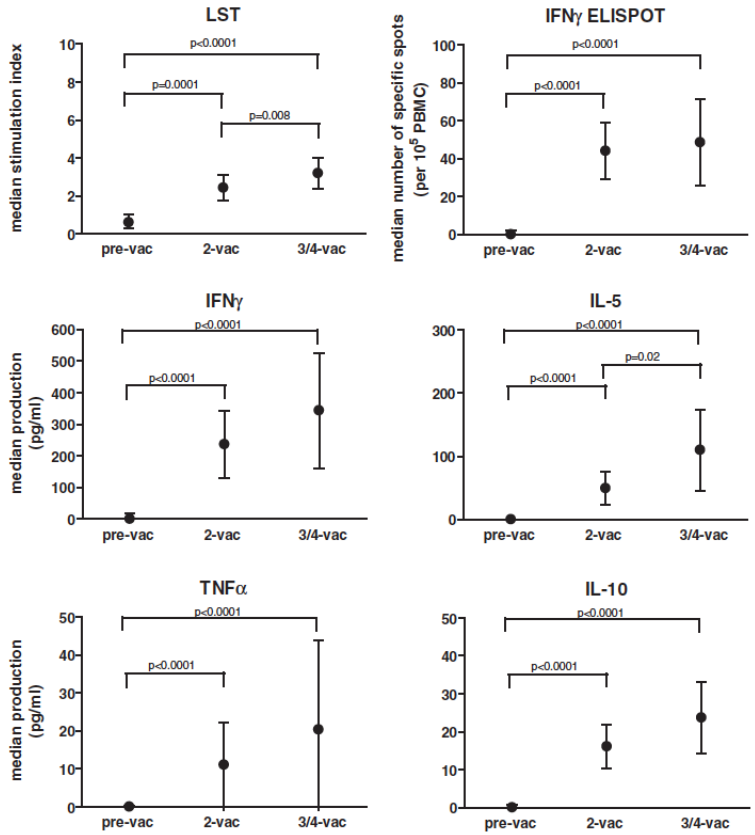
Table 3. Clinical Results at 3, 12, and 24 Months after the Last Vaccination.*

Patient No.	No. of Vaccinations	At 3 Months				At 12 Mo		At 24 Mo
		Symptoms	Lesion Response	Histologic Findings	Type of HPV Infection	Symptoms	Lesion Response	Lesion Response
1	4	Mild to moderate	Partial	VIN 2	16	Mild to moderate	Partial	Partial†
2	4	Severe	None	VIN 3	16		Carcinoma	
3	4	Severe	None	VIN 3	16	None	Partial	Partial‡
6	4	None	Complete	Normal	16	None	Complete	Complete
7	4	None	Complete	Normal	None	None	Complete	Complete
8	4	Mild to moderate	Complete	Normal	6b	None	Complete§	Complete
9	3	None	Complete	Normal	None	None	Complete	Complete
10	4	None	Partial	VIN 3	16	Lost to follow-up¶		
11	4	None	None	VIN 3	16	None	Complete	Complete
12	4	Mild to moderate	None	VIN 3	16	Mild to moderate	Partial	None‖
13	4	Mild to moderate	Partial	VIN 3	16	Mild to moderate	Partial	Partial
16	4	Mild to moderate	Partial	VIN 1	16	Mild to moderate	Complete	Complete
18	4	Severe	None	VIN 3	16	Severe	None	None
22	4	Mild to moderate	None	VIN 3	16	Severe	Partial	Partial
23	4	Mild to moderate	Partial	VIN 2	16	None	Partial	Microinvasive carcinoma**
26	4	None	None	VIN 3	16	None	None	None
27	3	None	Partial	VIN 3	16	None	Complete	Complete
28	4	None	None	VIN 3	16	None	None	None
29	4	None	Complete	Normal	None	None	Complete	Complete
30	4	Mild to moderate	Partial	VIN 2	16	None	Complete	Complete

Late disease setting: HPV16 vaccination for advanced cervical cancer



Van Poelgeest et al., J. Transl Med. 2013



RNA-encoded vaccines

Strategy:

» TAA encoded by mRNA

Advantages:

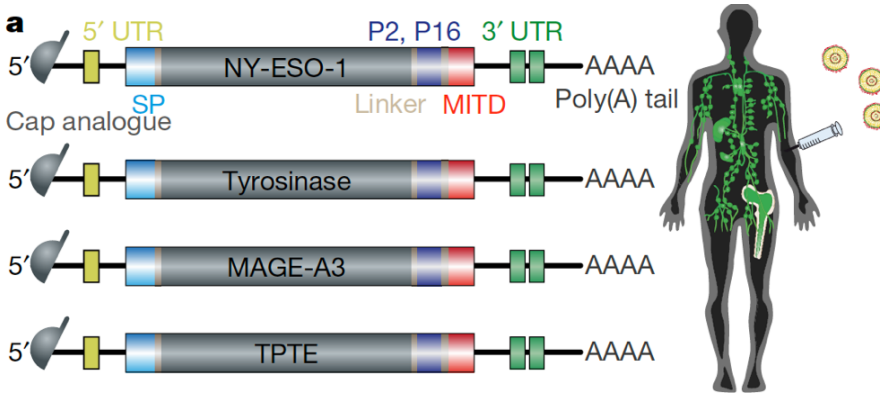
» RNA acts as an adjuvant

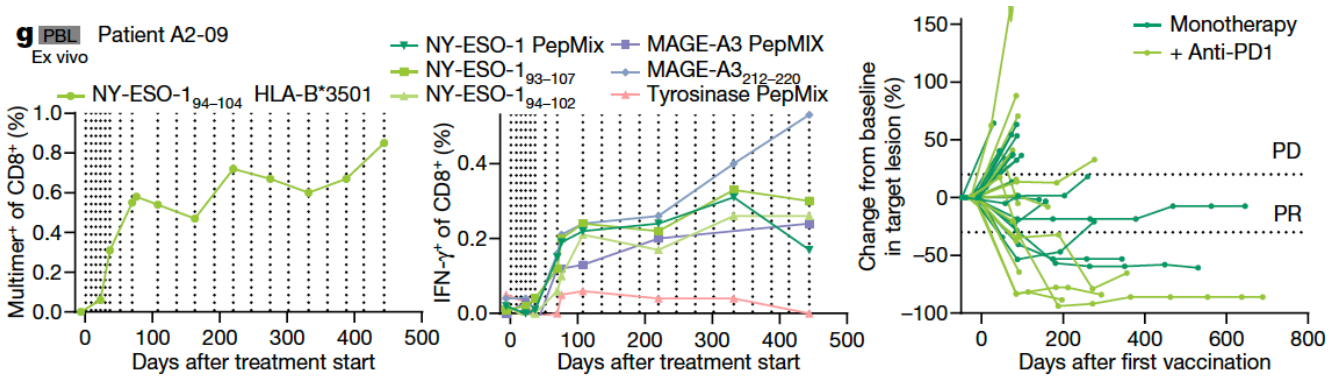
» Endogenous antigen processing, no MHC restriction

Example:

» Fixvac: RNA vaccine against TAA in melanoma

Sahin U et al., Nature. 585:107 (2020)





DNA-encoded vaccines

Strategy:

» TAA encoded by a DNA plasmid vector

Advantages:

» DNA acts as an adjuvant

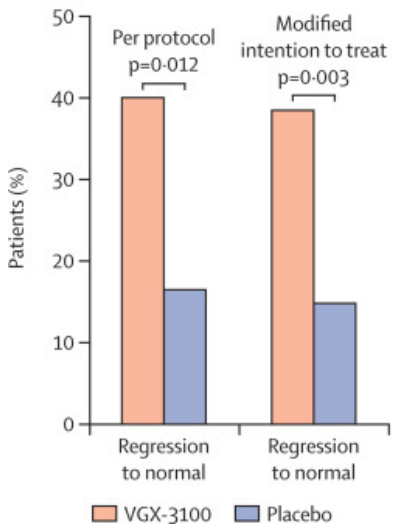
» Endogenous antigen processing, no MHC restriction

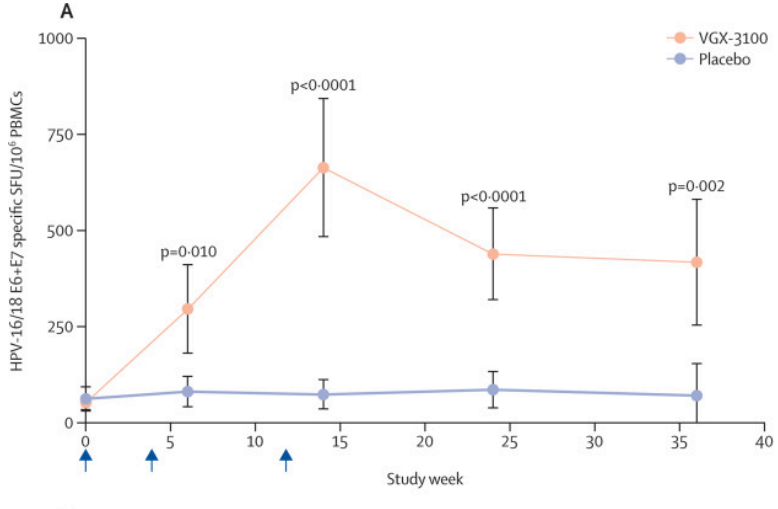
Disadvantages:

» Typically requires electroporation

Example:

» VGX3100: DNA vaccine against HPV16, 18 E6/E7 proteins in CIN2/3 patients

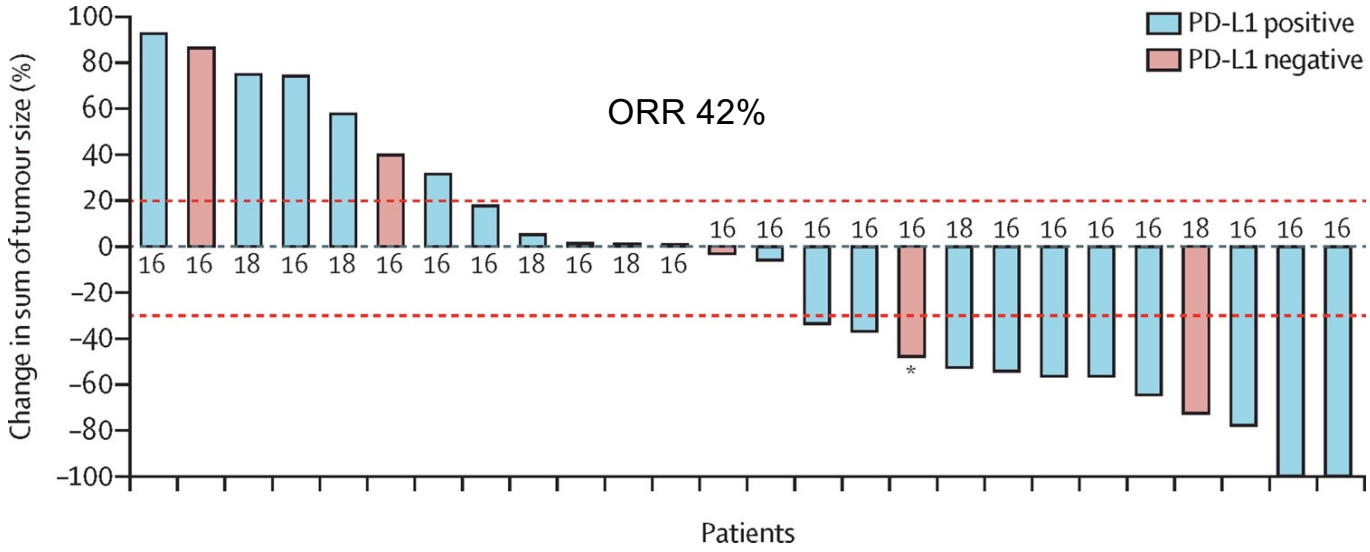




Sahin U et al., Nature. 585:107 (2020)

DNA-encoded vaccine against HPV 16 and HPV 18 (GX-188E) in combination with PD-1 blockade in advanced cervical cancer

(single-agent anti-PD-1 has ~15% response rate in PD-L1(+) cervical cancer, 0% response rate in PD-L1(-) cervical cancer)



Youn et al., Lancet Oncology 2020

Virus-vectored vaccines

Strategy:

» TAA encoded by a replicating or non-replicating virus vector

Advantages:

» Virus-induced activation of immune response acts as an adjuvant

Disadvantages:

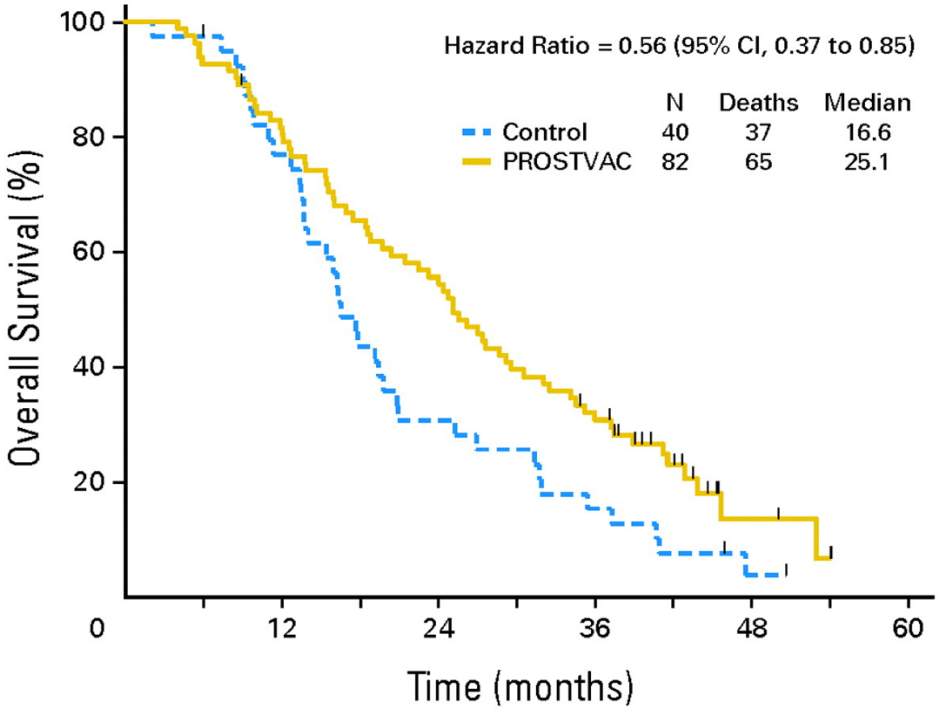
» Biosafety

» Infection concerns

Example:

» PROSTVAC (vaccine composed of two poxvirus vectors, vaccinia and fowlpox, encoding PSA, B7.1, ICAM-1, and LFA-3)

Kantoff et al., JCO 29:1099 (2010)



Bacteria-vectored vaccines

Strategy:

» TAA encoded by bacteria

Advantages:

» Bacteria-induced activation of immune response acts as an adjuvant

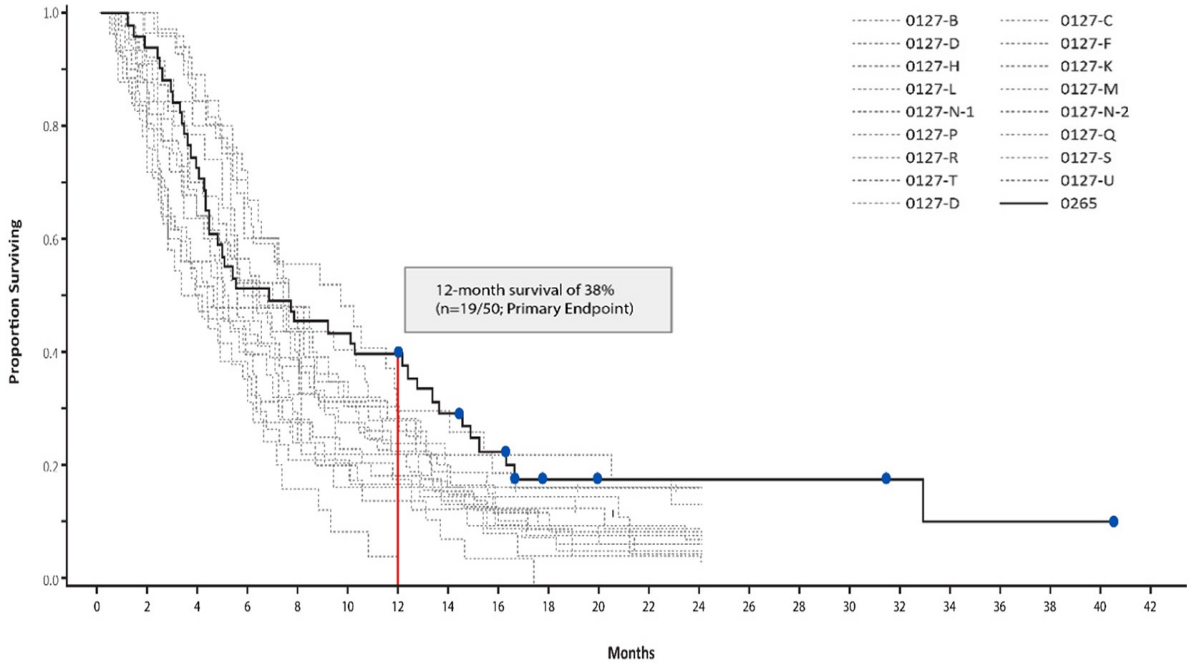
Disadvantages:

» Biosafety

» Infection concerns

Example:

» ADX-S11-001 – engineered Listeria monocytogenes expressing HPV16 E7 in cervical cancer



Huh W., et al. Gynecologic Oncology 2020

Cellular vaccines

Strategy:

» Autologous or allogeneic cancer cells modified to be more immunogenic

» Cells are inactivated (e.g. irradiated) prior to injection back into patients

» Allogeneic strategy relies on antigens shared among patients

Advantages:

» Potential for recognition of multiple tumor antigens

» Endogenous antigen processing, no MHC restriction

Disadvantages:

» Complex (for autologous); require fresh tumor resections

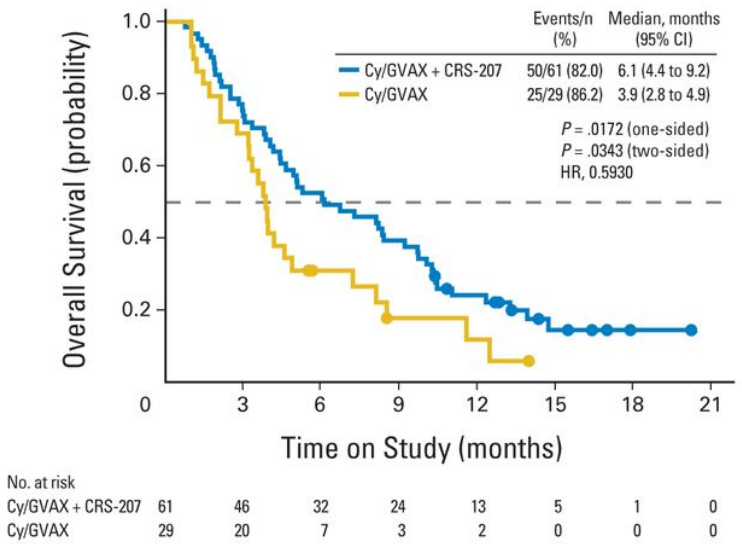
Example:

» GVAX – allogeneic tumor cell lines expressing GM-CSF.

Le D., JCO 2015

GVAX + CRS-207 prime-boost in pancreatic cancer

GVAX: Two irradiated allogeneic pancreatic cancer cell lines secreting GM-CSF
CRS-207: Recombinant attenuated Listeria monocytogenes expressing mesothelin (a TAA commonly expressed in pancreatic cancer)



Dendritic cell (DC) vaccines

Strategy:

» PBMC-derived autologous DCs pulsed with tumor antigen (peptide, protein, RNA, DNA, inactivated tumor cells)

Advantages:

» Potential for recognition of multiple tumor antigens (depending on strategy)

» Endogenous antigen processing, no MHC restriction

» Bypasses the need for in vivo antigen uptake by DCs

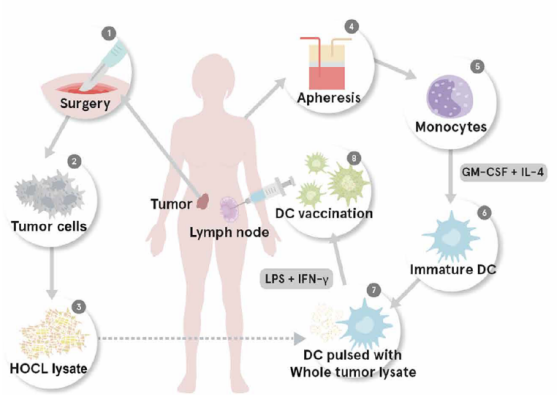
Disadvantages:

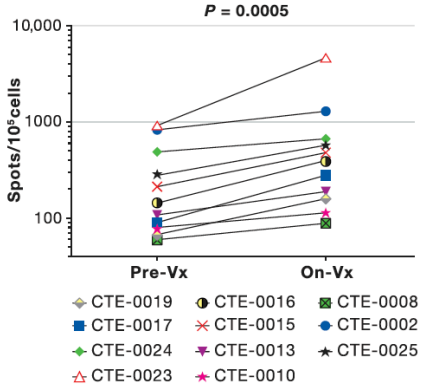
» Complexity of preparation

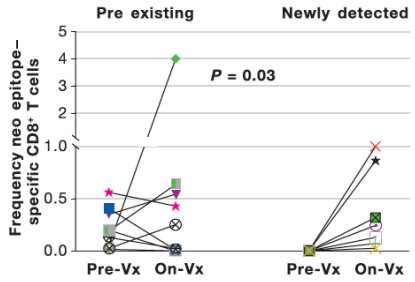
Example:

» OCDC in ovarian cancer

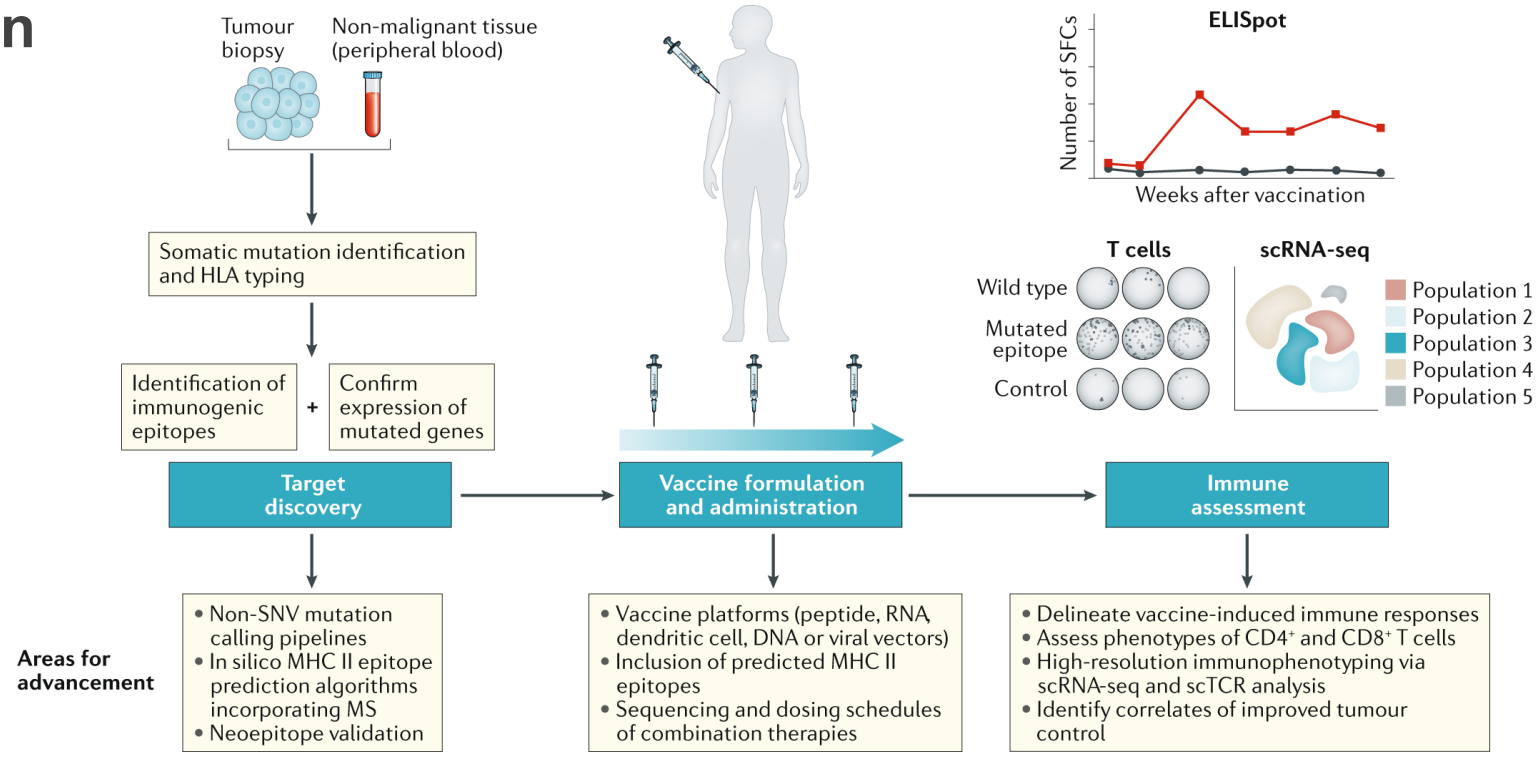
Tanyi et al., Sci. Transl. Med. (2018)







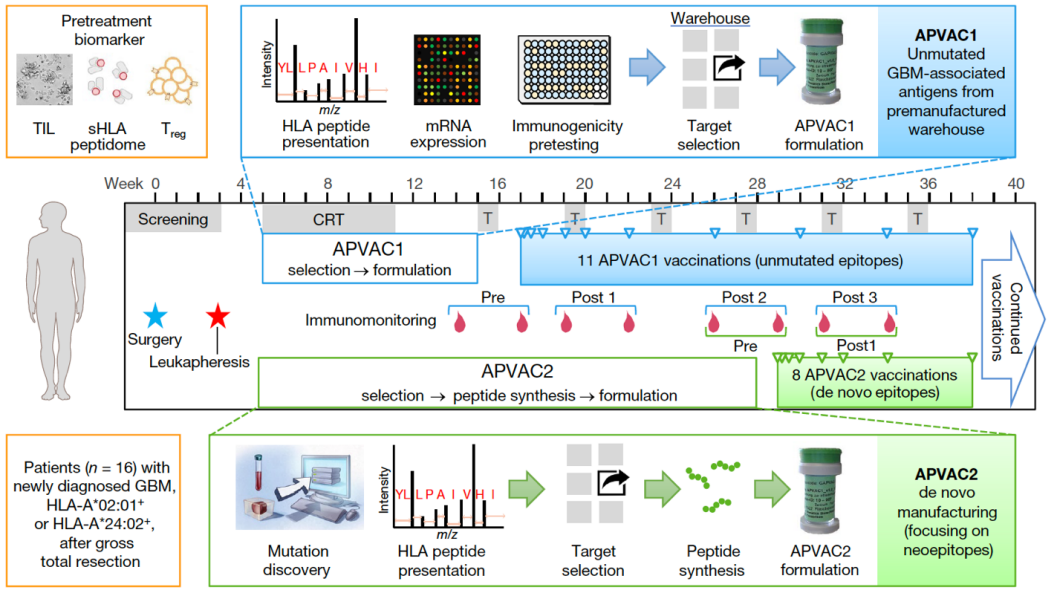
Neoantigen vaccines

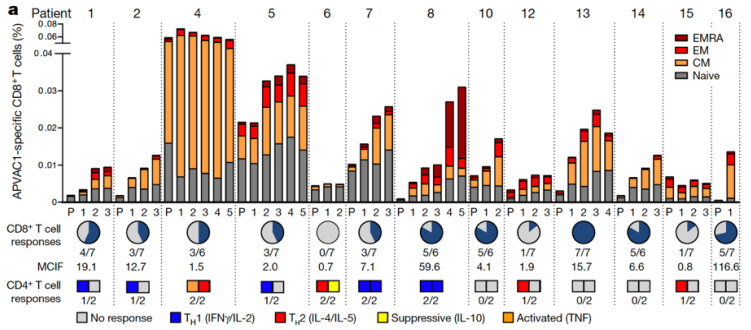


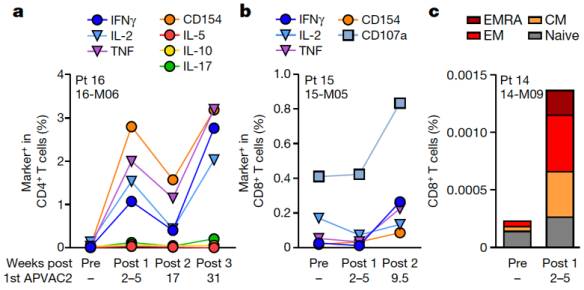
Blass E and Ott P. Nat. Rev. Clin. Oncol. 2021

Neoantigen vaccines

Public (APVAC1) and private (APVAC2) vaccination in patients with newly diagnosed glioblastoma

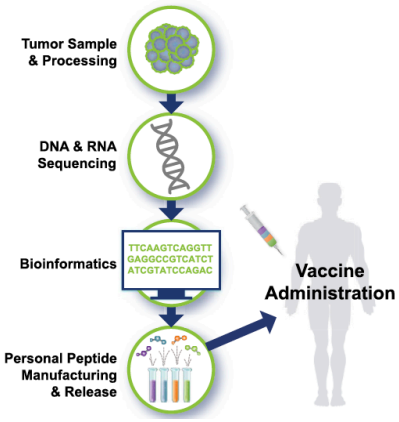


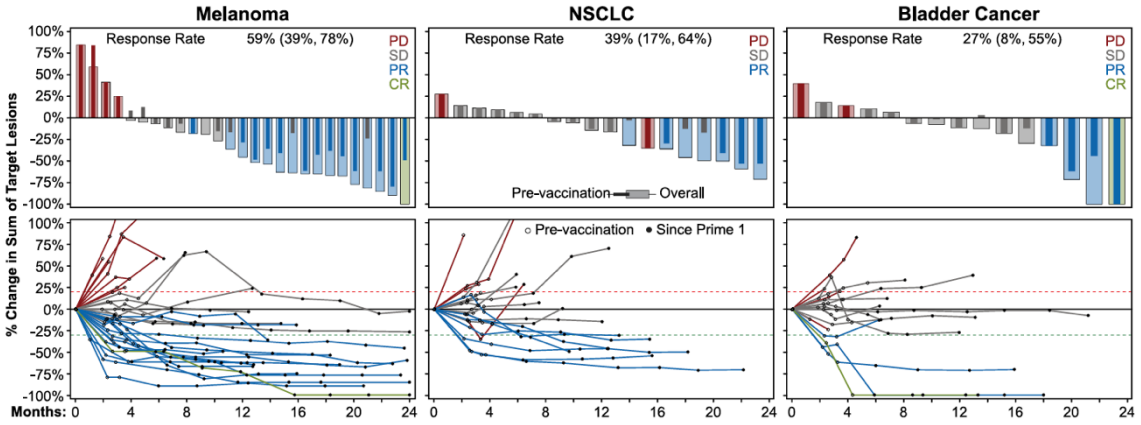


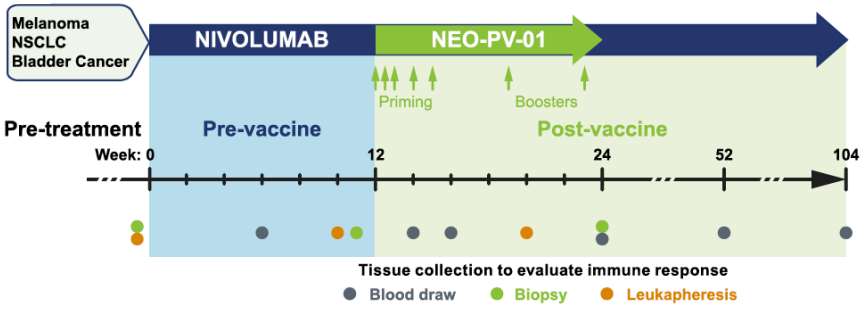


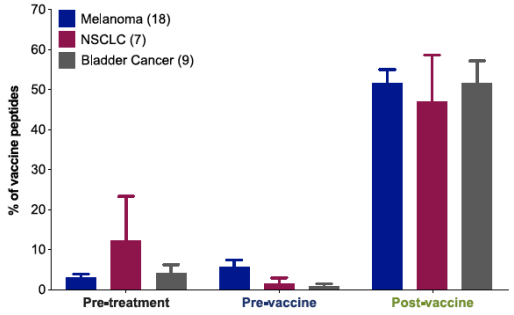
Hilf N et al., Nature. (2018)

Neoantigen vaccines in combination with PD-1 blockade









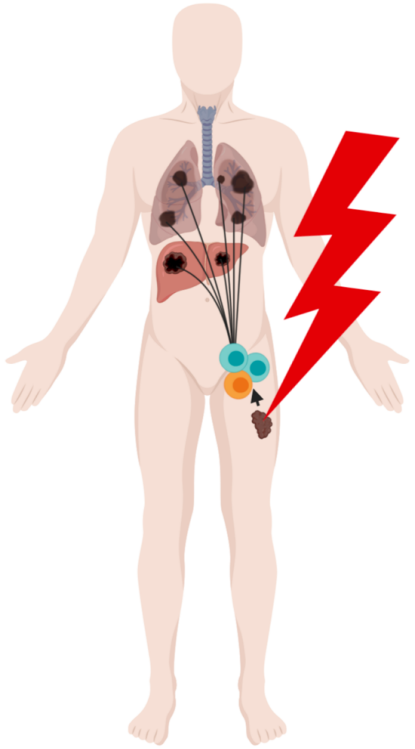
Ott P et al., Cell 2020

In situ vaccination

Goal: generate localized antigen release and activation of antigen presenting cells leading to systemic T cell response

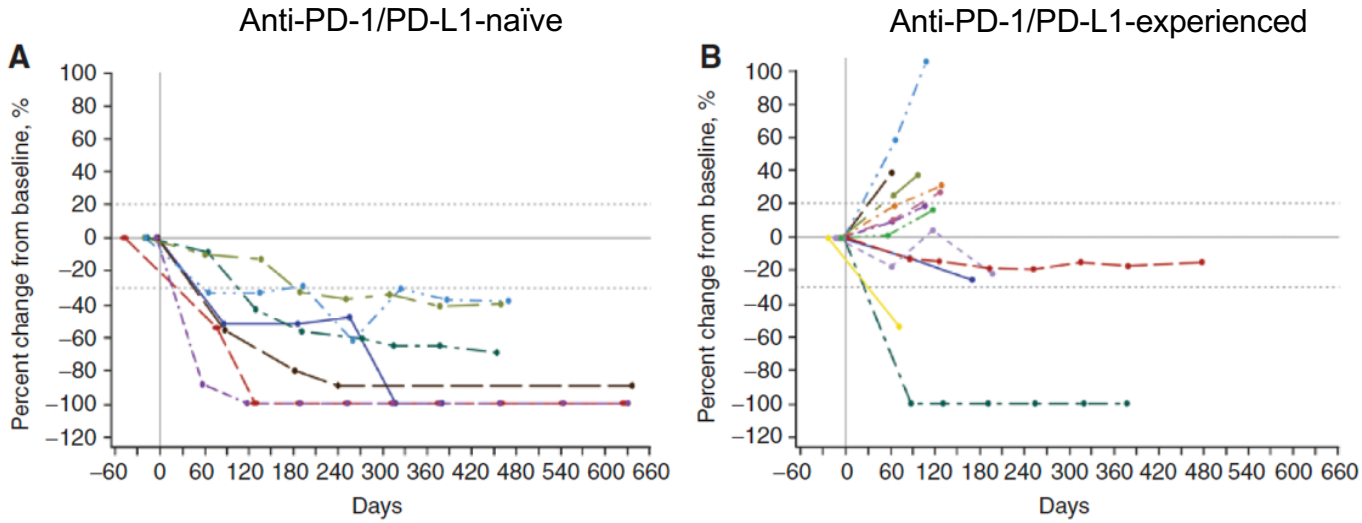
Exploit broad TAA repertoire available at the tumor site

- Local ablative therapies (radiation, cryotherapy, microwave ablation, etc.)
- Intratumoral cytokine injection (e.g. IL-12)
- Intratumoral co-stimulatory ligand injection (e.g. CD40 agonist)
- Intratumoral TLR agonist injection (e.g. TLR3,7,8,9)
- Intratumoral STING agonist injection
- Intratumoral injection of bacteria (e.g. Clostridium novyi)
- Intratumoral injection of viruses (e.g. Talimogene laherparepvec)



TLR agonists in combination with PD-1 blockade

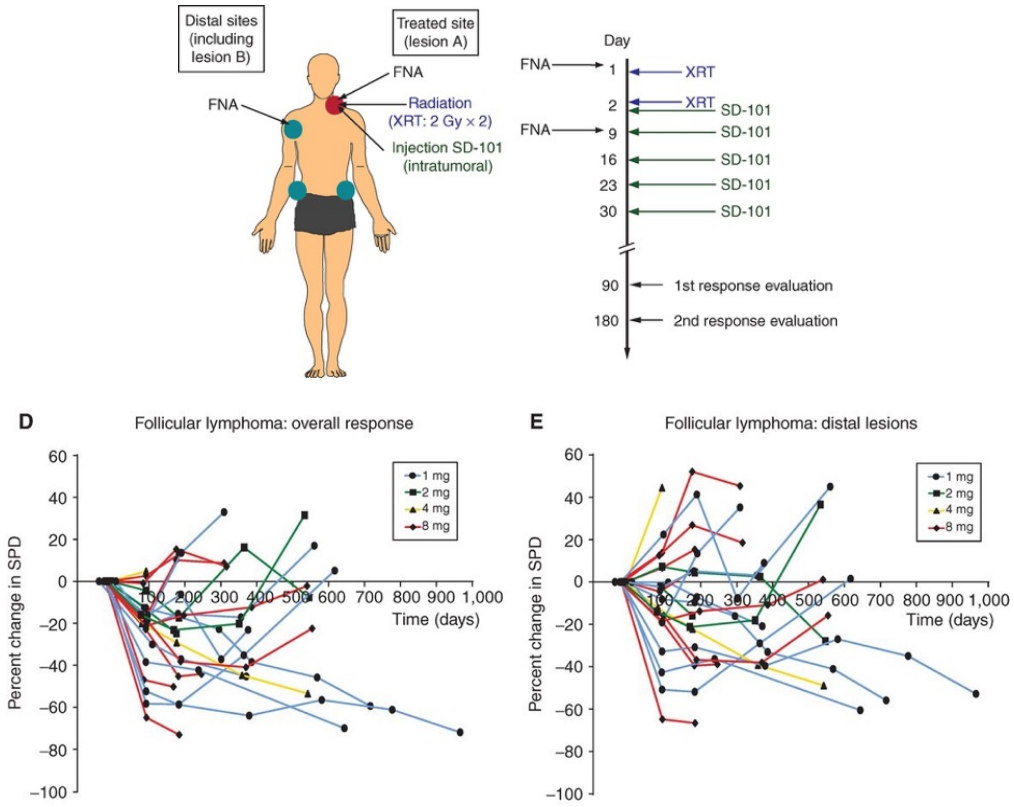
Intratumoral SD-101 (TLR9 agonist) in combination with PD-1 blockade in patients with anti-PD-1-naïve and anti-PD-1-refractory melanoma



Ribas et al., Cancer Discovery 2018

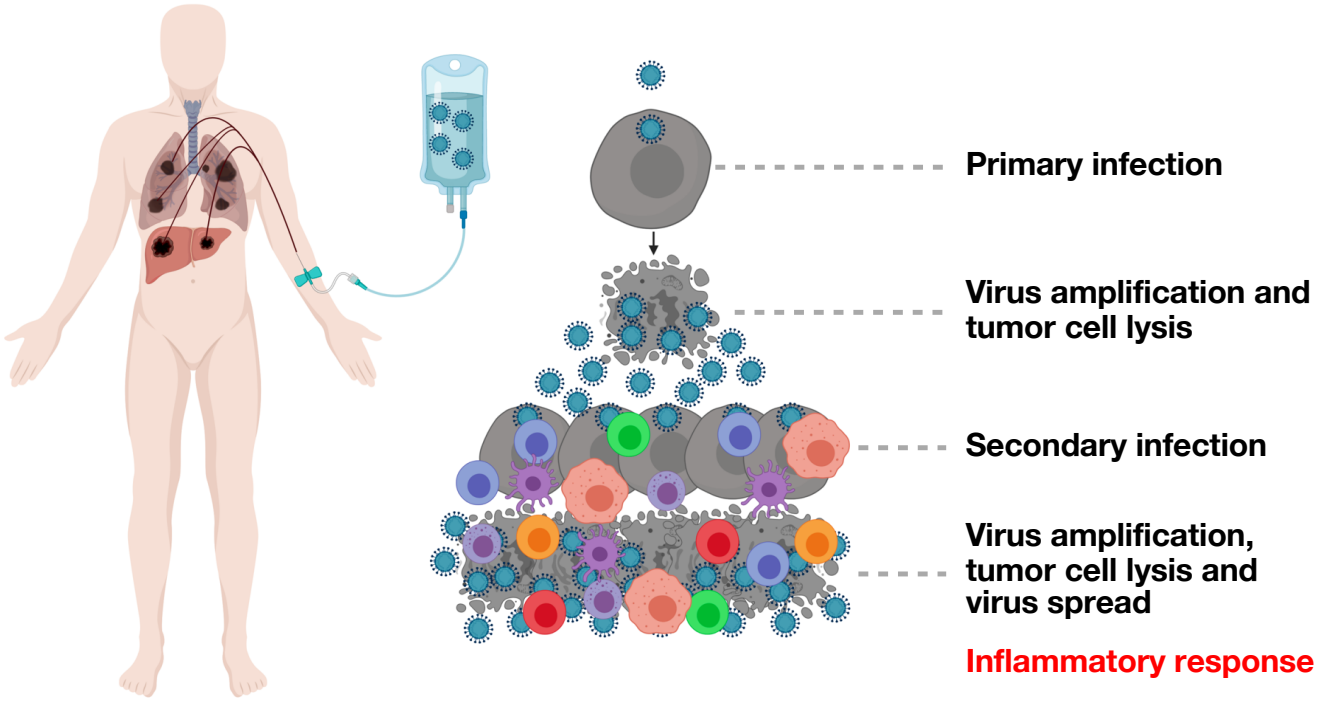
TLR agonists in combination with PD-1 blockade

Intratumoral SD-101 (TLR9 agonist) in combination with radiation in patients with untreated indolent lymphoma



Frank et al., Cancer Discovery 2018

Oncolytic viruses have predilection for replication and lysis of cancer cells over normal cells



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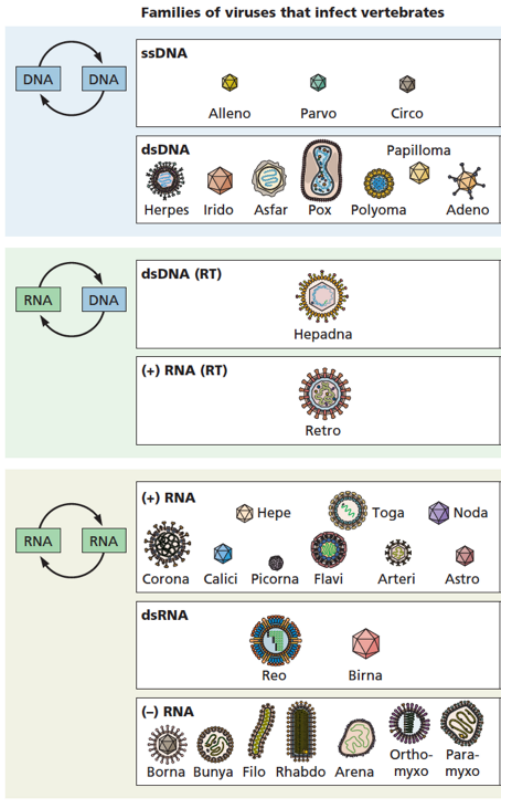
Each virus type exhibits unique biology, which dictates pathogenicity, host and tissue tropism, immune response, and potential for therapeutic application

[1]Principles of Virology, 4th edition
[2]Vile, R. Molecular Therapy. 2014.

1



2


Wild-type virus

Fatal disease:measles, polio, smallpox

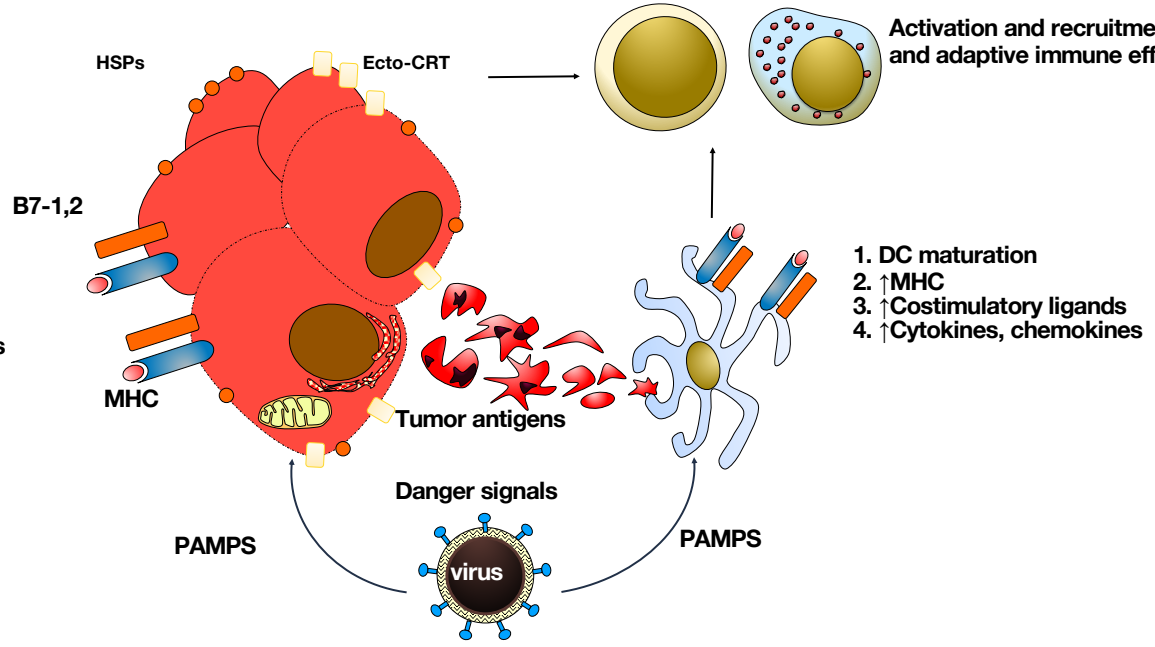
Attenuation: Oncolytic Virus

Arming: Oncolytic Virus with Teeth

Treating disease: cancer

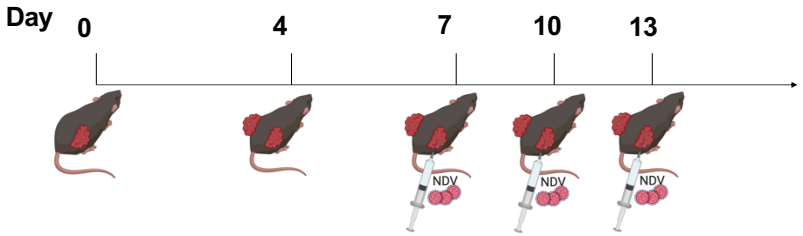
Oncolytic viruses don't just lyse cancer cells, they make them more immunogenic

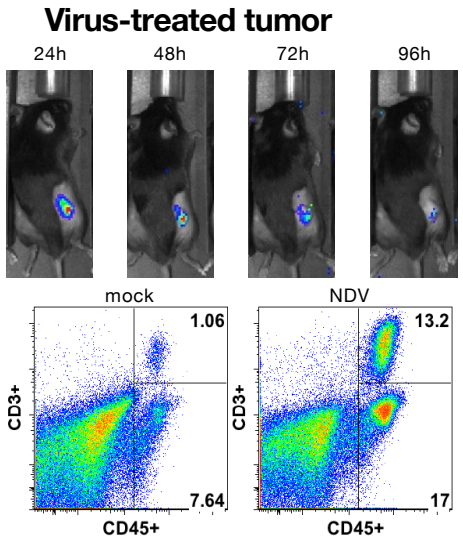
1.↑MHC,
2.↑Costimulatory ligands
3.↑Surface HSPs
and ecto-CRT
4.↑Type I IFN

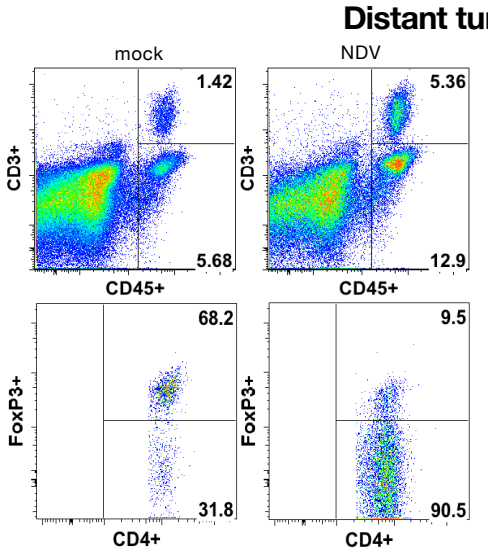


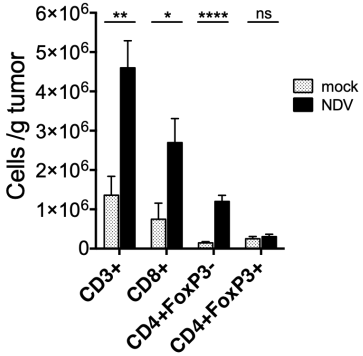
Zamarin D. and Wolchok J.D., Molecular Therapy-Oncolytics 1 (2014)

Intratumoral oncolytic viruses induce systemic immunity



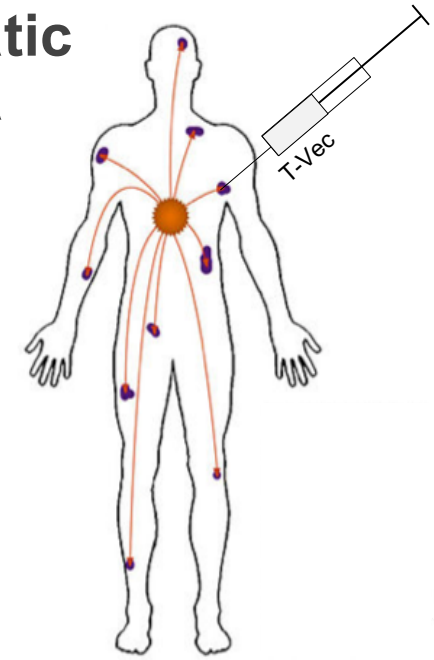


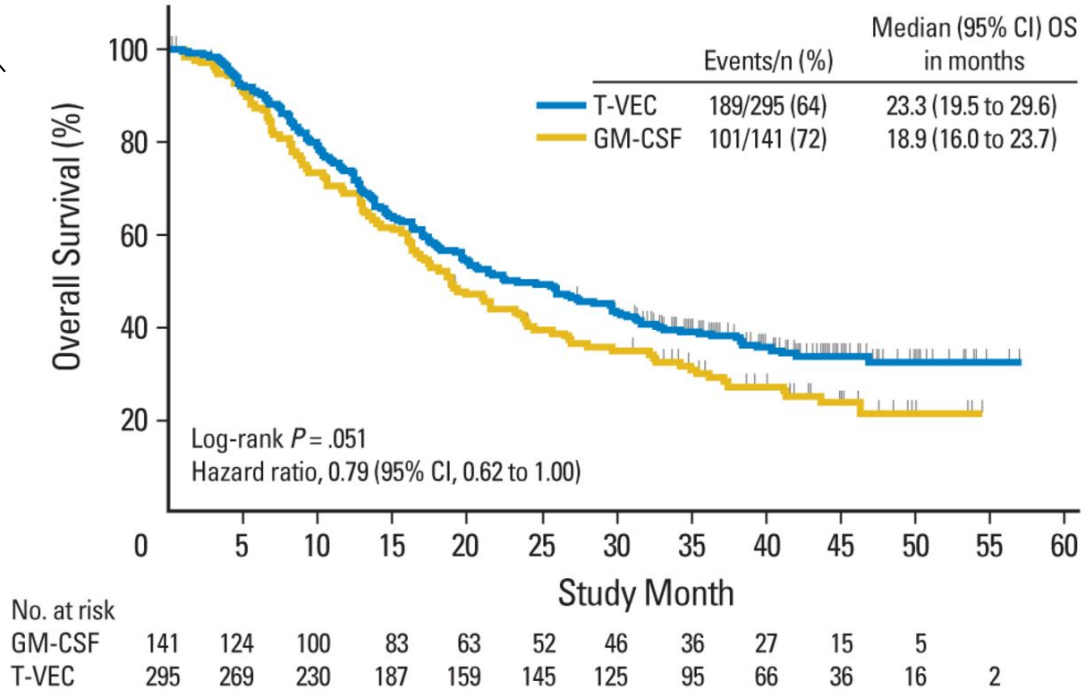




Zamarin D, Wolchok JD, Allison JP. Sci. Transl. Med. 2014 5:226ra

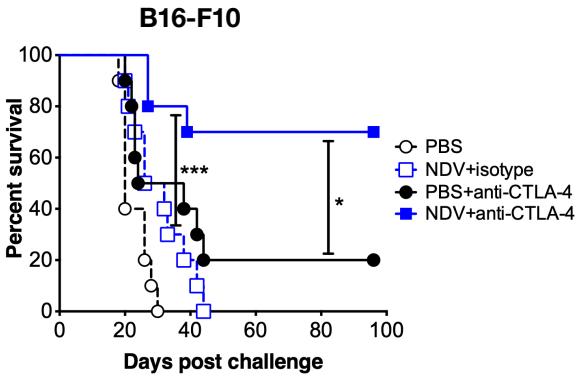
Talimogene laherparepvec in metastatic melanoma

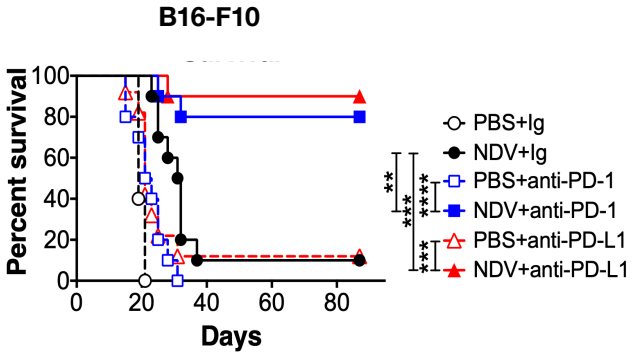


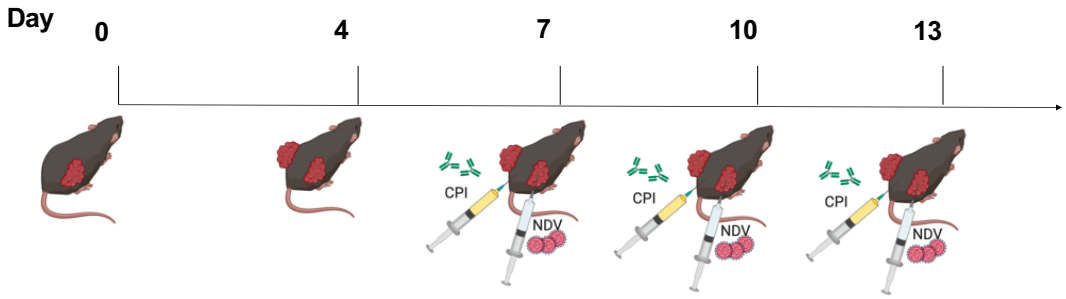


Andtbacka et al., J. Clin. Oncol. 33:2780 (2015)

Combination therapy with oncolytic viruses and CTLA-4 or PD-1/PD-L1 blockade leads to rejection of the treated and distant tumors

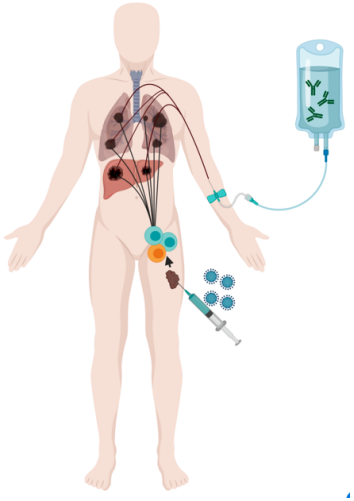




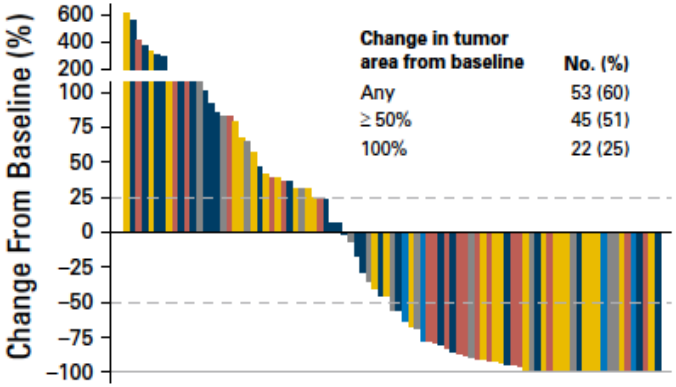


Zamarin D, … Wolchok JD, Allison JP. Sci. Transl. Med. 2014
Zamarin D,… Merghoub T, Wolchok JD. J. Clin. Invest. 2018
Zamarin D, … Wolchok JD, Allison JP. Nature Commun. 2017
Oseledchyk A., … Zamarin D. Oncotarget 2018.

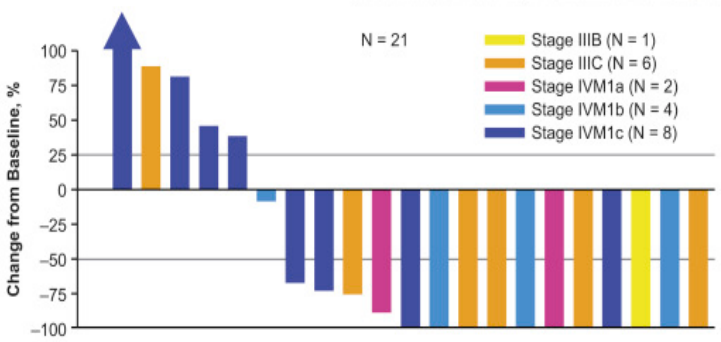
Oncolytic viruses potentiate the efficacy of anti-CTLA-4 and anti-PD-1 therapy in melanoma patients



Tvec + ipilimumab (anti-CTLA-4) (ORR 39%)[1]

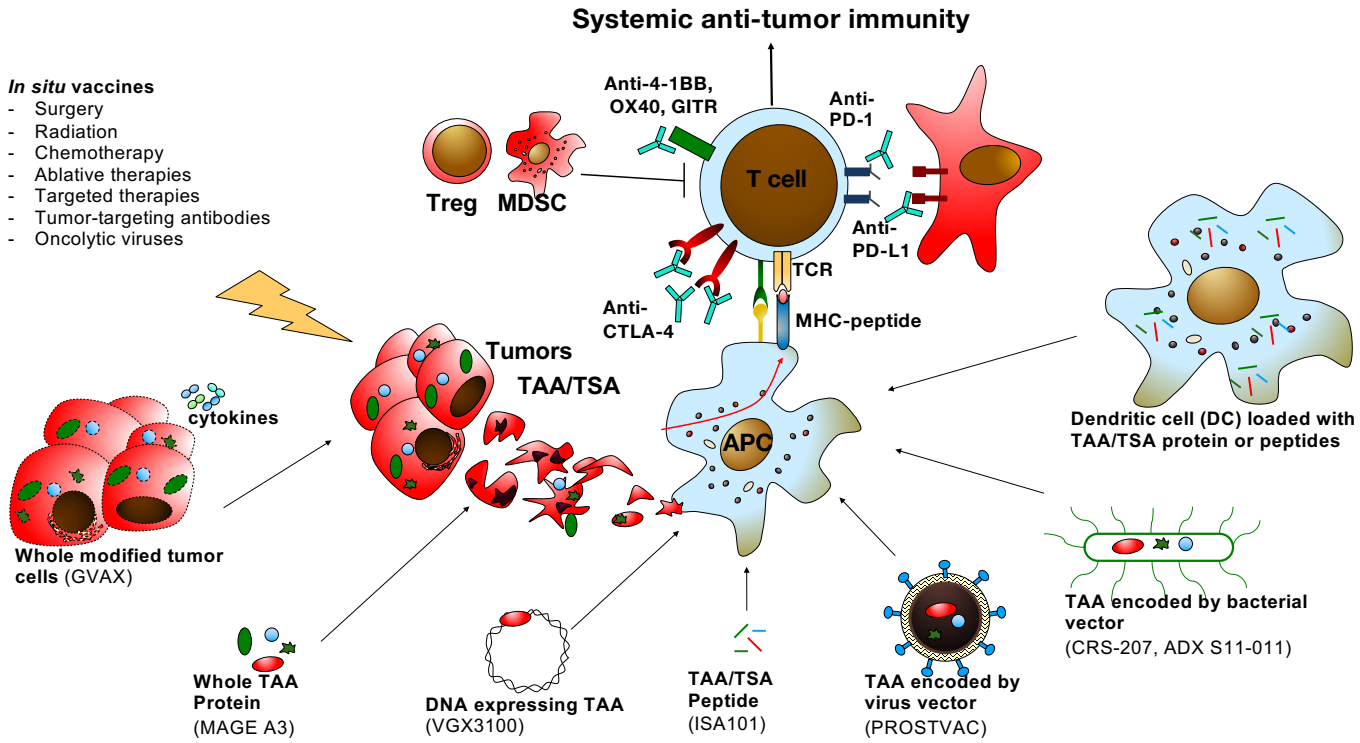


Tvec + pembrolizumab (anti-PD-1) (ORR 62%)[2]



[1]Chesney et al, JCO 2017
[2]Ribas et al, Cell 2017

Optimal therapeutic response to vaccines will require combinations with other agents



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Summary

- Adaptive immune response is dependent on the recognition of tumor-associated antigens and tumor-specific antigens
- Tumor vaccines aim to amplify pre-existing T cell response against tumor antigens or induce *de novo* T cell response
- Tumor vaccines come in many forms, including peptides, nucleic acid - encoded vaccines, cellular vaccines, and vectored vaccines
- Tumor vaccines require adjuvants for activation of antigen-presenting cells
- Neoantigen vaccines are personalized to patient tumor, but challenges exist in prediction/identification of antigenic targets and vaccine preparation
- In situ vaccines explore a broad repertoire of antigens present at the tumor site and rely on the immune system to "pick" the most immunogenic antigens
- Oncolytic viruses represent a class of in situ vaccines combining multiple features, including tumor lysis, activation of APCs, and delivery of immunostimulatory ligands/cytokines into tumors
- Optimal therapeutic responses to vaccines require combination strategies focusing on optimization of immune response and overcoming the suppressive tumor microenvironment

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Cancer Vaccines and Locoregional Immunotherapies

Questions