Cancer Vaccines

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The following relationships exist related to this presentation:

No relationships to disclose

Low anti-tumor activity of previous vaccine trials

35 reports of vaccine trials that included 765 patients considered representative of the majority of published trials

- RR: 3.8%
  - 7/175 (4.0%) patients treated with peptide vaccines
  - 6/142 (4.2%) patients treated with whole tumor cell vaccines
  - 14/198 (7.1%) patients treated with dendritic cell vaccines

Rosenberg, Yang, Restifo, *Nat Med*. 2004

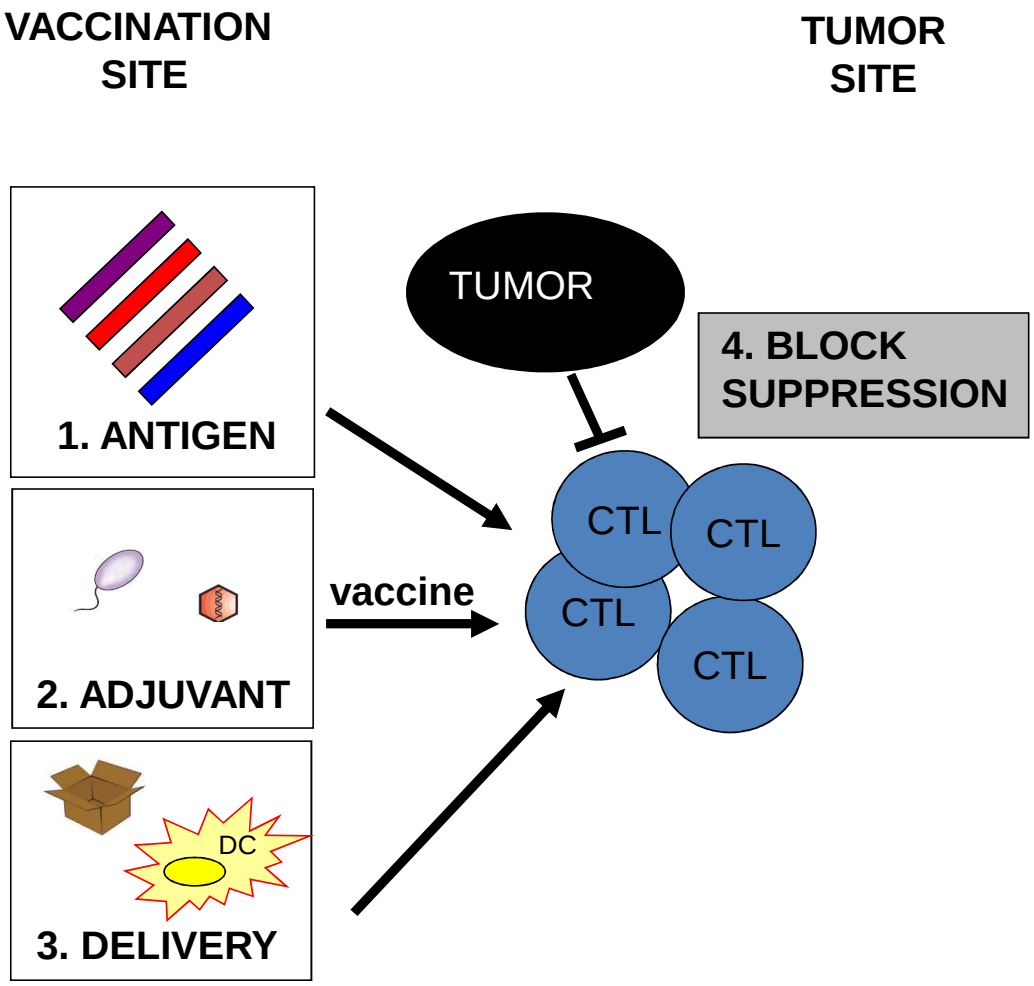
Cancer Vaccines: Why have they not worked (for the most part)

- Paucity of truly foreign antigens
- Immunosuppressive tumor microenvironment
- Lack of “inflammatory cues”
- Relatively poor understanding of how to induce strong and sustained T-cell–mediated immune responses against tumors in humans

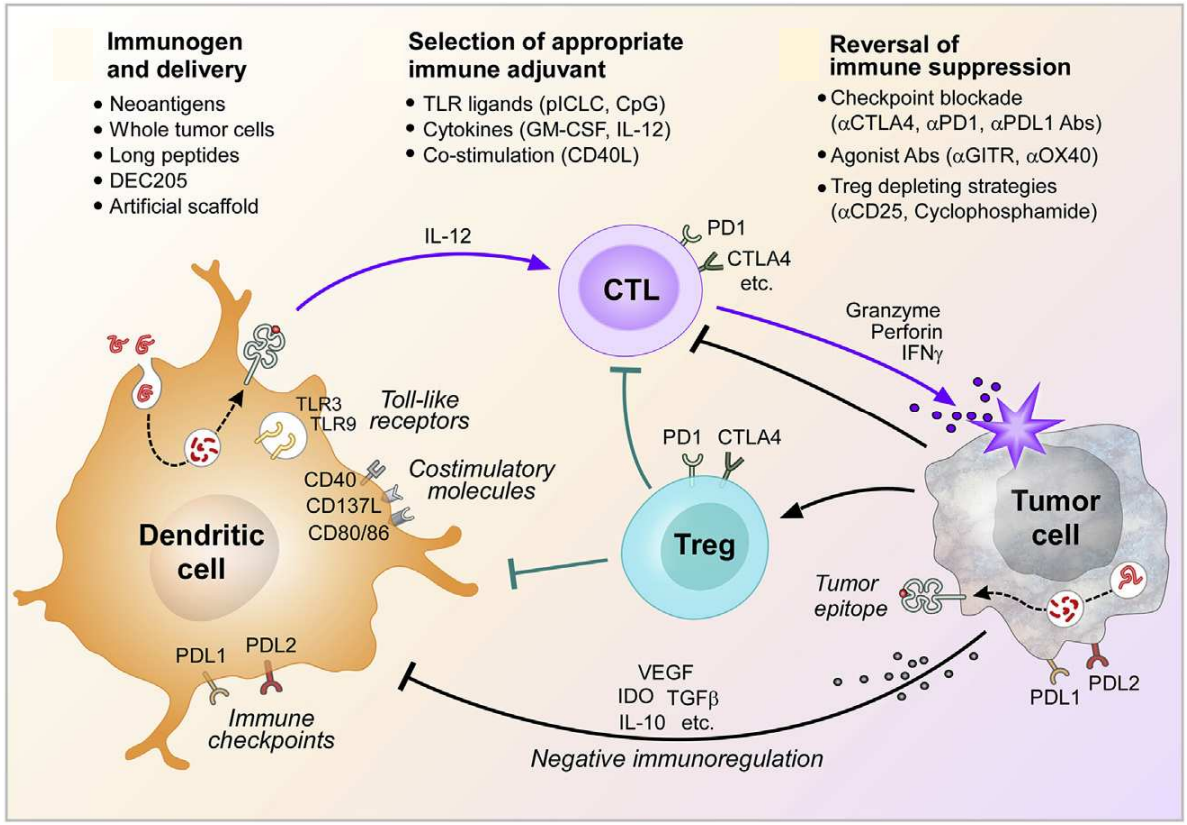
Cancer Vaccines: Renewed Interest

Recent rapid advancements in the field:

- Strategies to overcome regulatory/suppressive mechanisms:
  - PD-1/PD-L1 inhibition
  - IDO suppression
  - T reg suppression
- Effective targeted therapies for combination with immunotherapy
  - BRAF/MEK inhibition for melanoma
  - ALK inhibition for NSCLC
- Powerful genomic sequencing capabilites – neoantigens

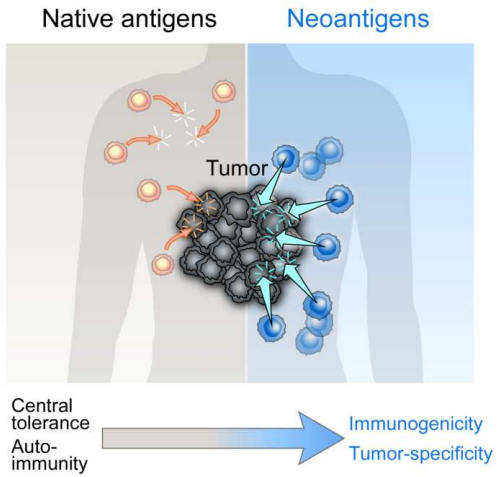

VACCINATION SITE
TUMOR SITE
1. ANTIGEN
2. ADJUVANT
3. DELIVERY
DC
vaccine
TUMOR
4. BLOCK SUPPRESSION
CTL
CTL
CTL
CTL

Important features of an effective cancer vaccine



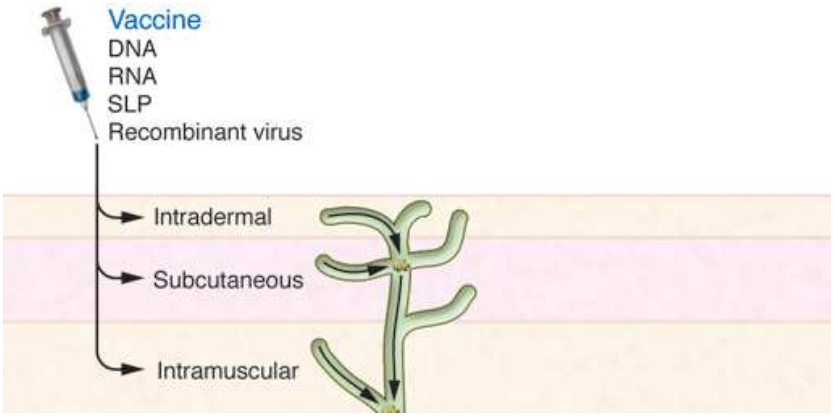
Ott et al. *Hematol Oncol Clin N Am* 2014

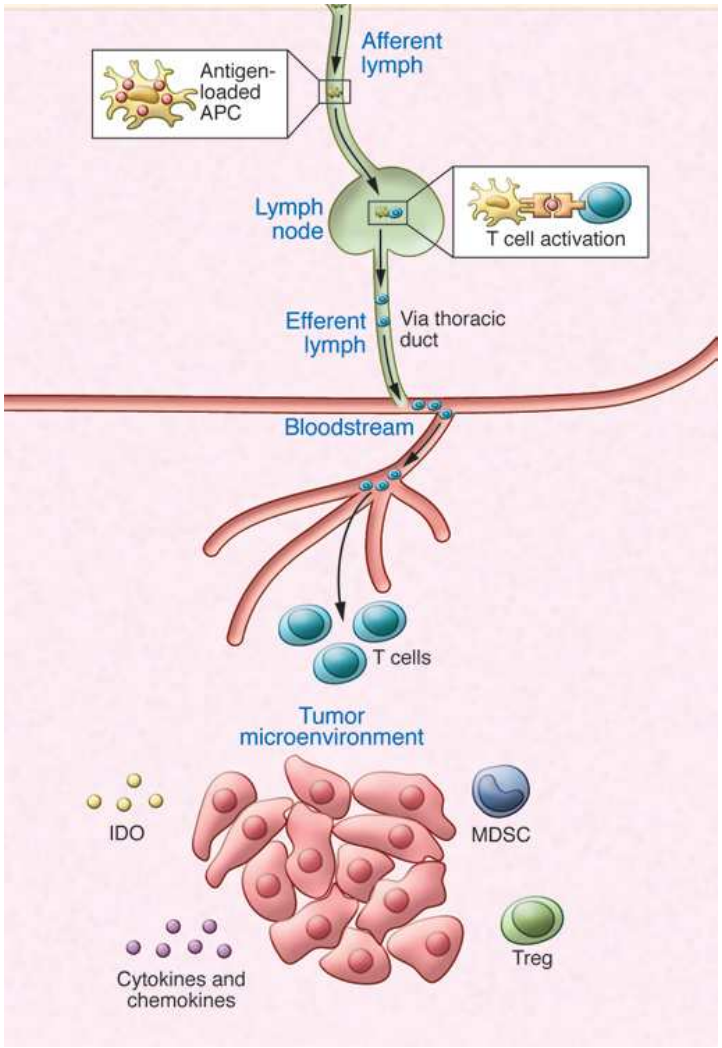
Immunogen



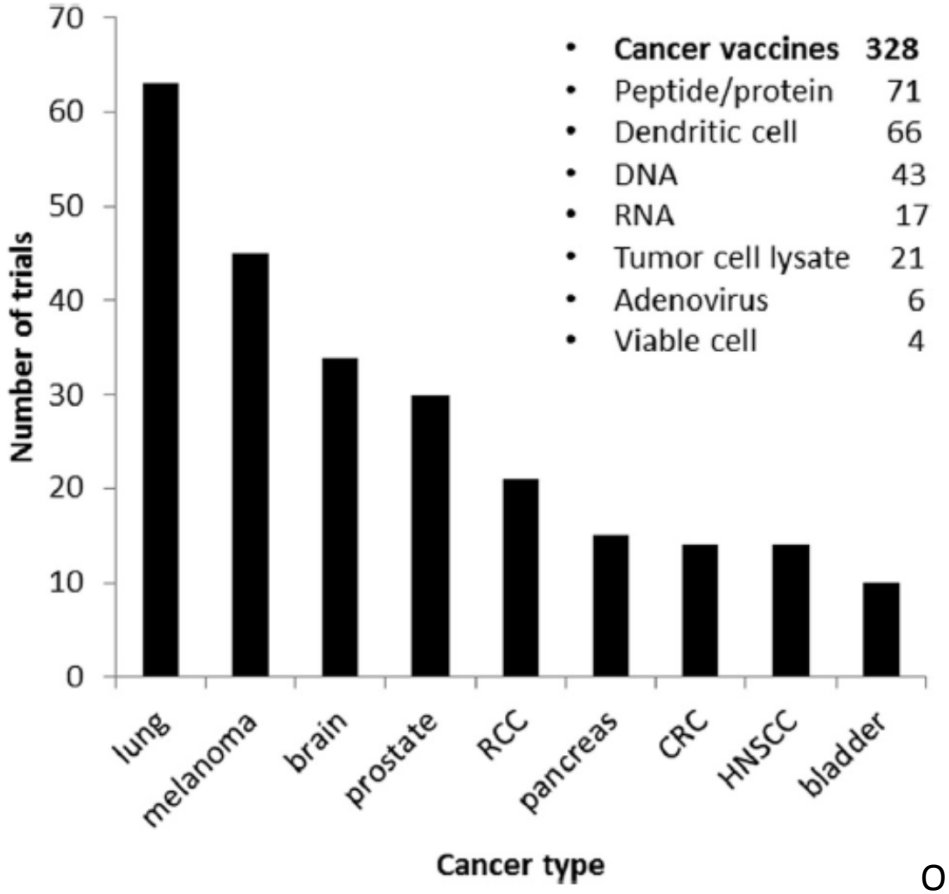
- Choice of Antigen
  - Differentiation antigen (MART-1, gp100)
  - Cancer testis antigen (NY-ESO-1, MAGE)
  - Overexpressed in tumors (KIT, HER2)
  - Mutated antigen (Neoantigen)
- Choice of Format:
  - Protein (broader antigenic selection)
  - Peptide (more stable in vivo, lower cost, HLA restriction). Long versus short
  - Viral vector
  - DNA, RNA
  - Whole tumor cells
  - Dendritic cells pulsed with protein or peptide

Routes of vaccine administration and migration of immune cells





Cancer Vaccine Trials

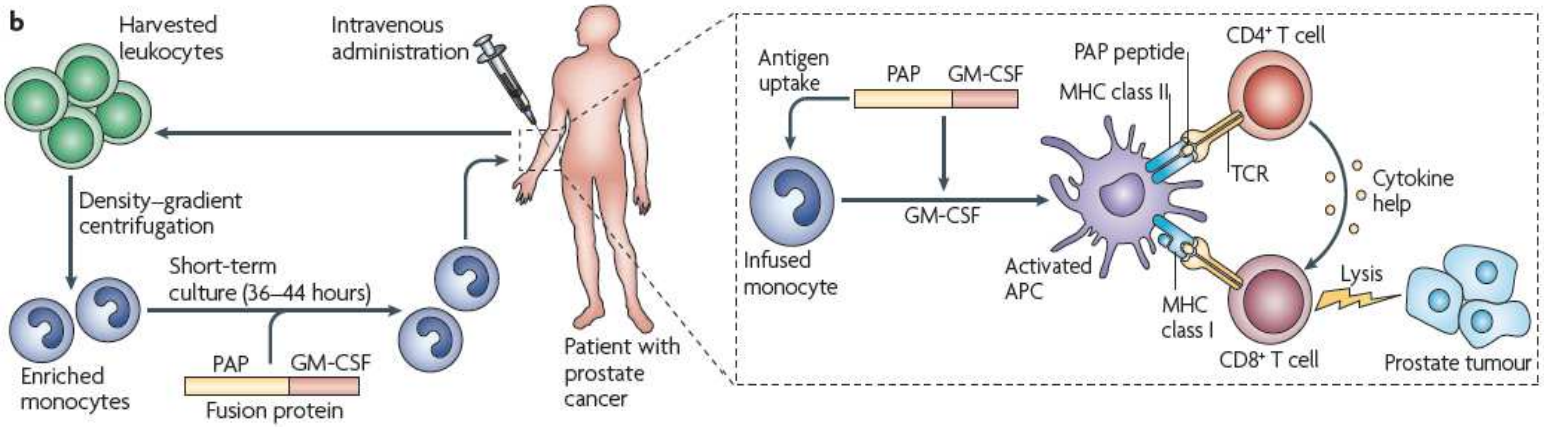


Obeid, *Sem. Oncol,* 2015

Cancer Vaccines in Late Stage Development / approved

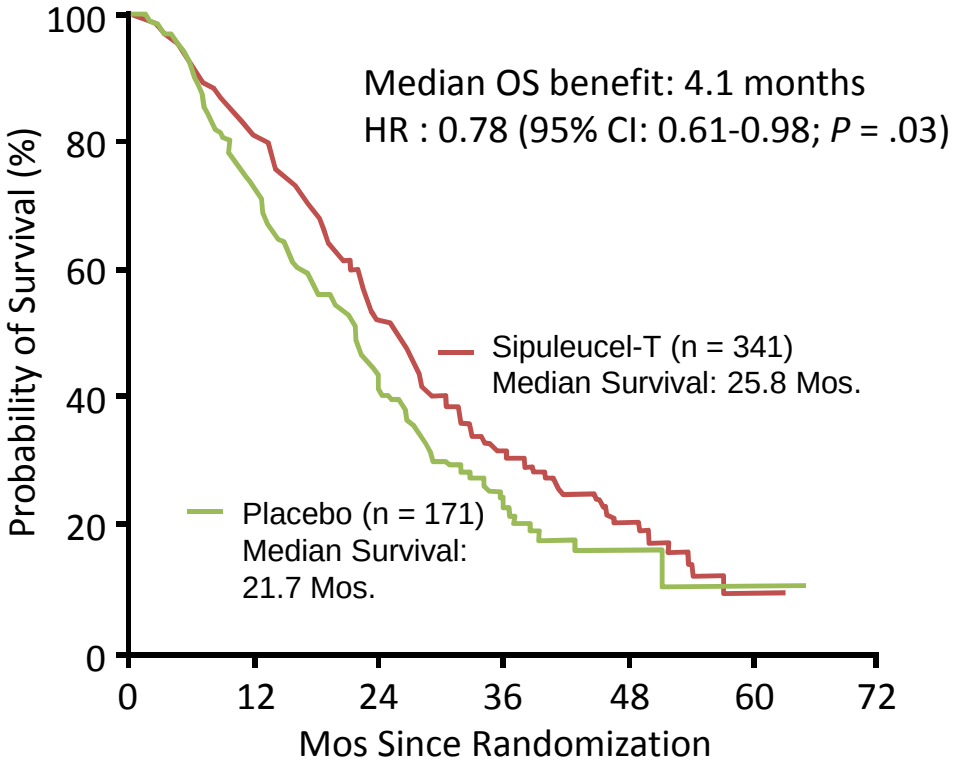
Name	Tumor	Antigen	Antigen Delivery	Immune Response	Clinical Activity
Siplileucel-T	Prostate Ca	PSA	Cell based - Monocytes	Yes	Yes – FDA approved
GVAX + CRS-207	Pancreatic Cancer	Mesothelin	Live attenuated listeria, prime - boost	Yes	Yes
IMA 901	Renal Cell Carcinoma	Tumor associated peptides (TUMAP)	Peptides with GM-CSF	Yes	Yes
Synthetic Long E6/7 Peptide vaccine HPV-01	HPV-induced malignancies (e.g vulvar neoplasia)	HPV E6 and E7	Mixture of 13 long peptides (25-35 AA)	Yes	Yes
Talimogene Laherparepvec (TVEC)	Melanoma	“Whole tumor” (in situ vaccination with onclytic virus)	Oncolytc virus (modified herpes virus encoding GM-CSF)	Yes	Yes - FDA approved
Rindopepimut	Glioblastoma	Mutated EGFRvIII	14-mer peptide, KLH	Yes	Yes
Fowlpox-PSA-TRICOM	Prostate Ca	PSA	Fowlpox expressing antigen + TRICOM (B7.1, ICAM-1, LFA-3)	Yes	Yes

Sipuleucel-T: Vaccination With Fresh (Functional) APCs: Generate ex vivo and Reinfuse



Drake, Nat Rev Immunol. 2010.

Phase III Trial of Sipuleucel-T Immunotherapy in mCRPC (IMPACT): OS



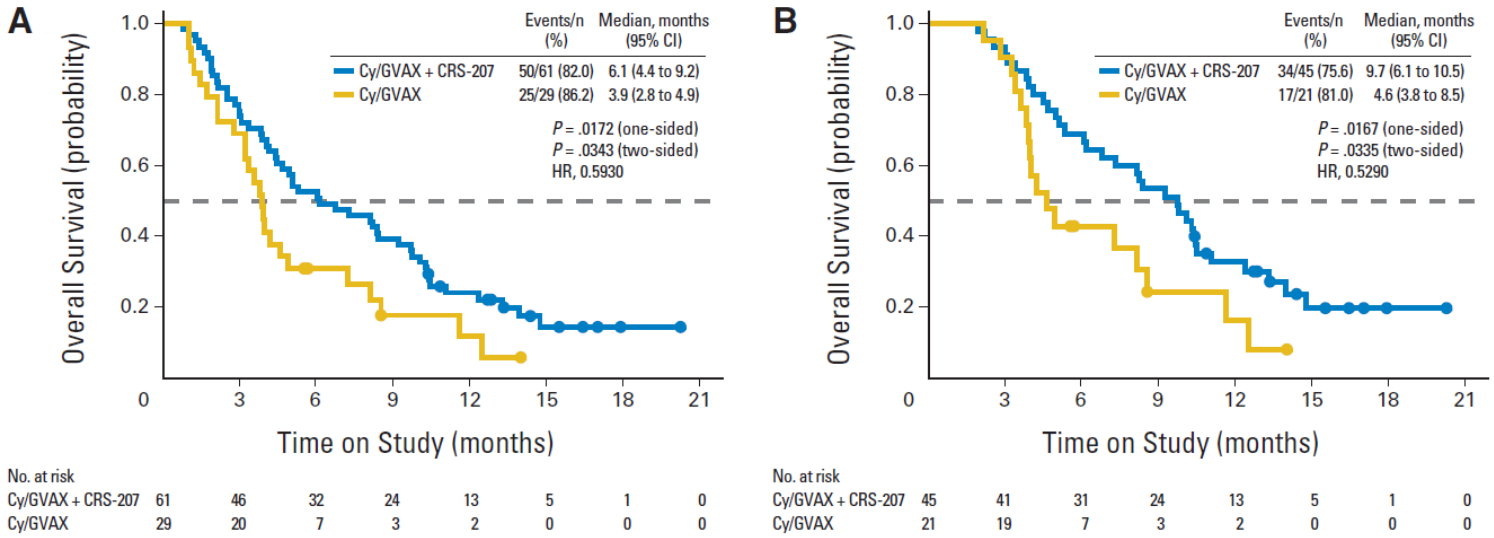
Kantoff PW, et al. N Engl J Med. 2010

Phase 2 GVAX pancreas and CRS-207 immunotherapy versus GVAX alone in pancreatic adenocarcinoma

- GVAX:
  - irradiated, GM-CSF-secreting allogeneic pancreatic cancer cell lines given intradermally
- CRS-207:
  - live-attenuated *Listeria monocytogenes* (Lm) which expresses mesothelin and stimulates innate and adaptive immunity.
- Low-dose cyclophosphamide (CY):
  - given prior to GVAX to inhibit regulatory T-cells.

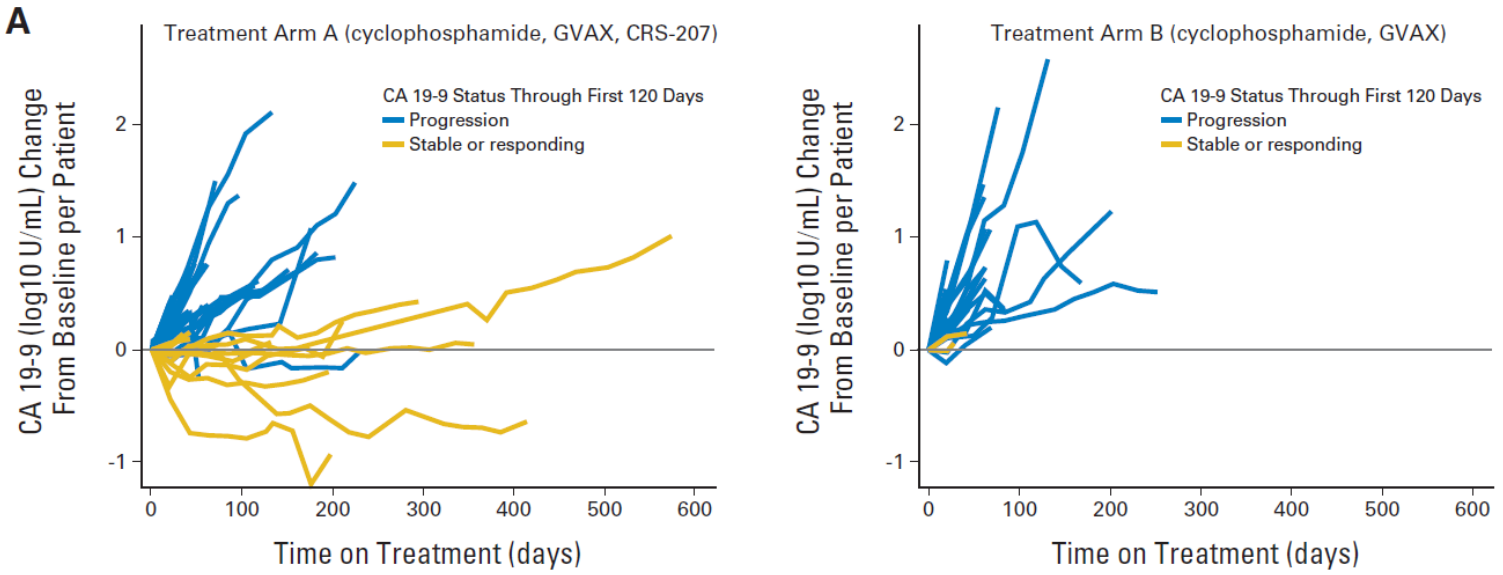
Le, *J Clin Oncol* 2015

Phase 2 GVAX pancreas and CRS-207 immunotherapy versus GVAX alone in pancreatic adenocarcinoma



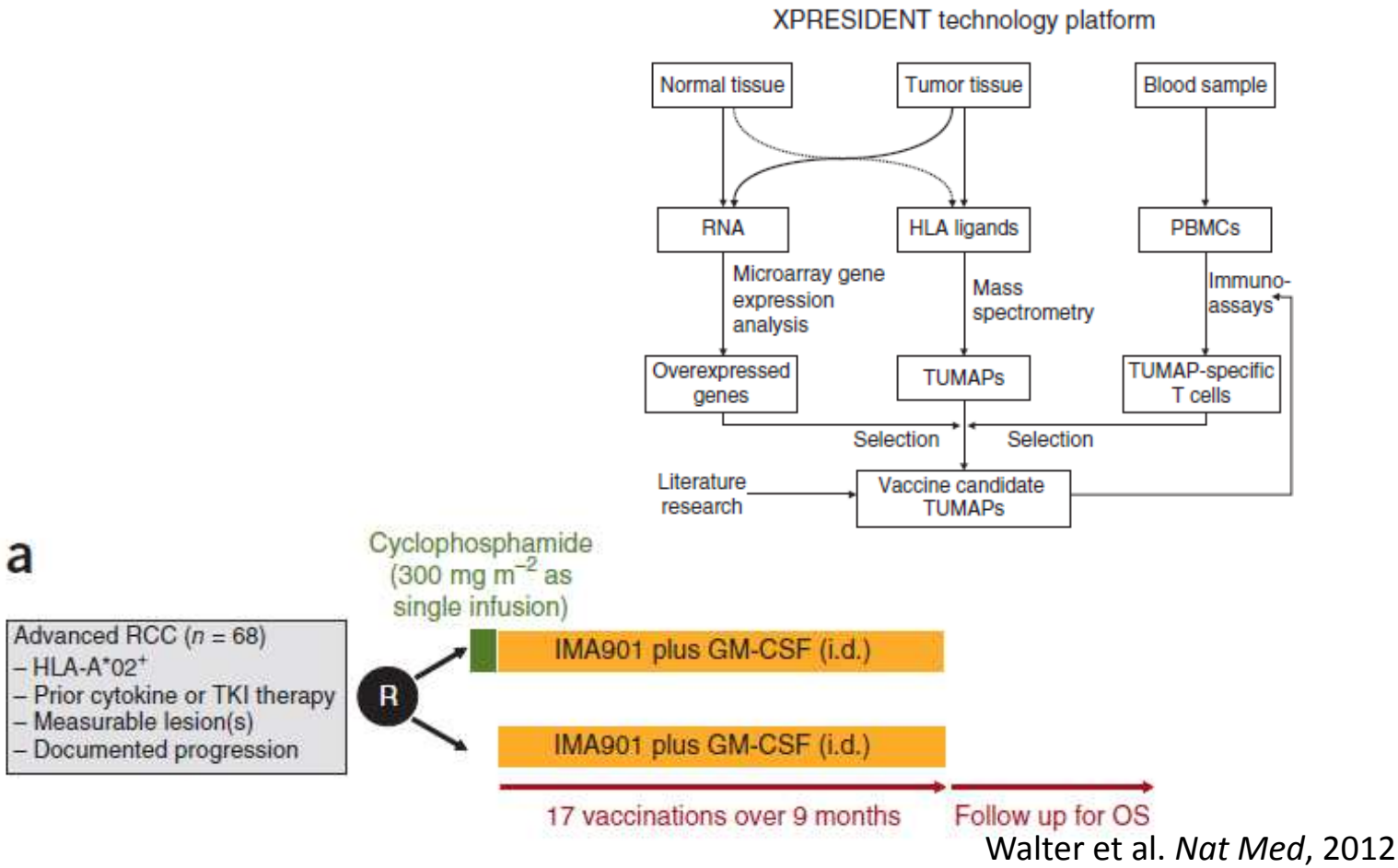
Le, *J Clin Oncol* 2015

Phase 2 GVAX pancreas and CRS-207 immunotherapy versus GVAX alone in pancreatic adenocarcinoma



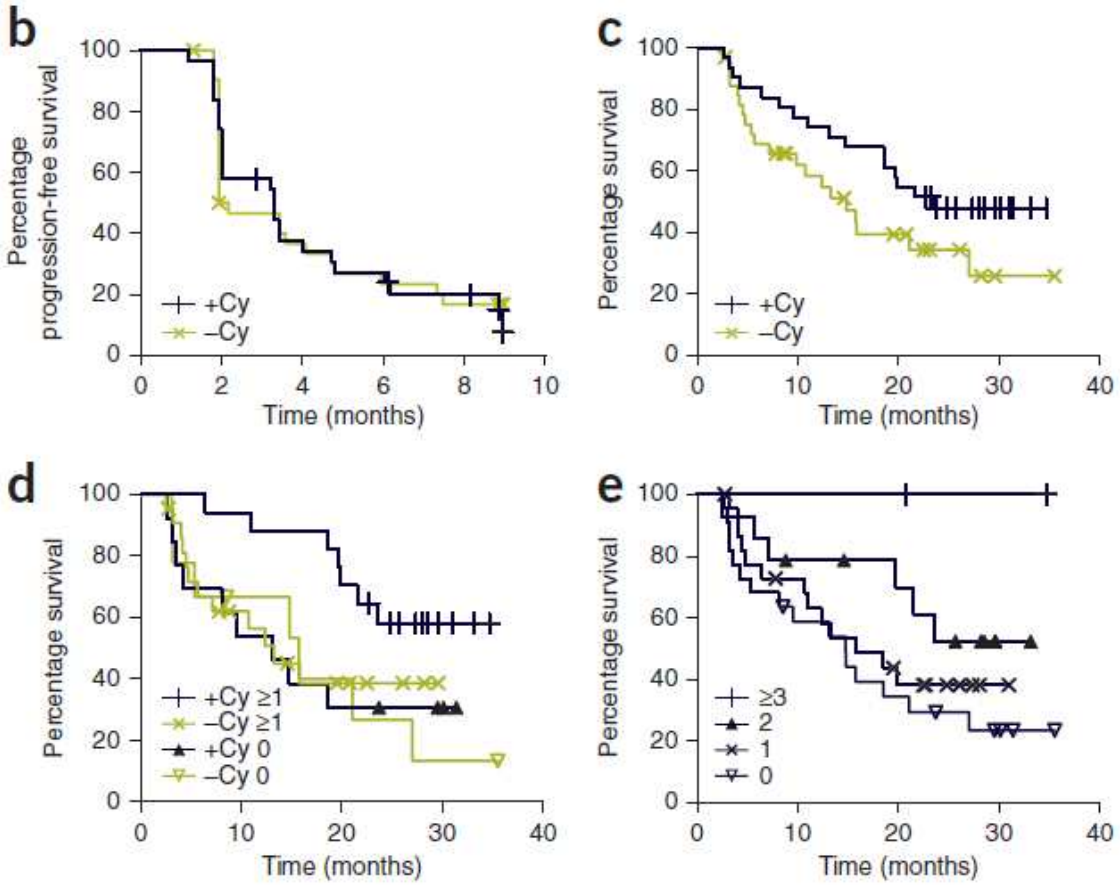
Le, *J Clin Oncol* 2015

Multipeptide cancer vaccine IMA901



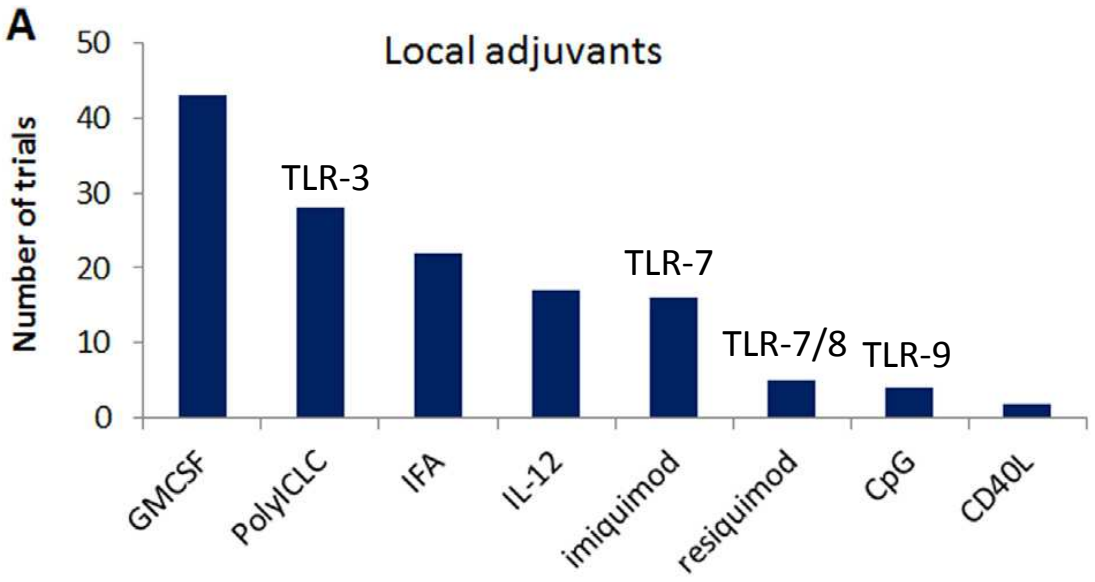
Walter et al. *Nat Med*, 2012

Immune response and to IMA901 and Treg depletion associated with improved Overall Survival



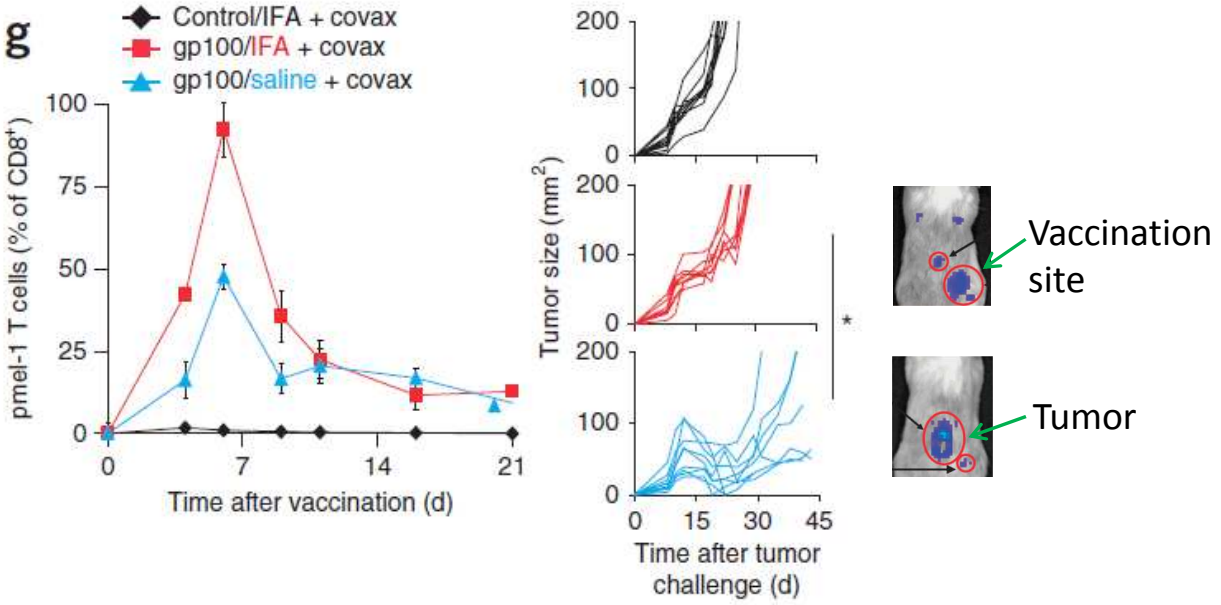
Walter et al. *Nat Med*, 2012

Adjuvants used in Cancer Vaccine Trials



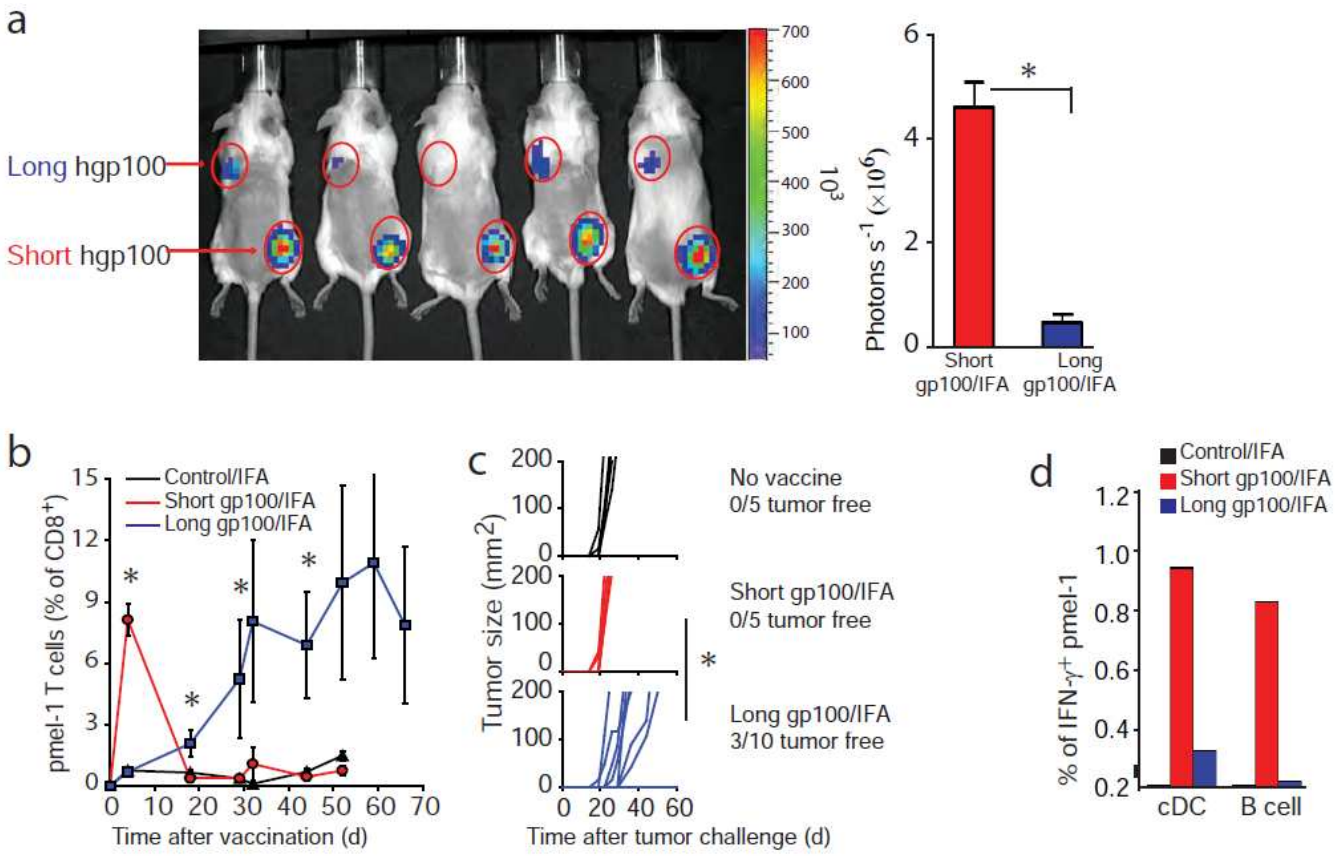
Obeid, *Sem. Oncol,* 2015

Persistent antigen at vaccination site compromises anti-tumor CD8-T cell responses



Hailemichael, *NEJM,* 2013

Short peptides versus long peptides



Hailemichael, *NEJM,* 2013

Toll Like Receptor Agonists

Danger is represented by:

These have molecular features that distinguish them from our own cells:

endotoxin

DS RNA

HMGB1

binds RAGE, LPS; amplifies TLR signal

lipopeptides

CpG DNA

SS RNA

flagellin

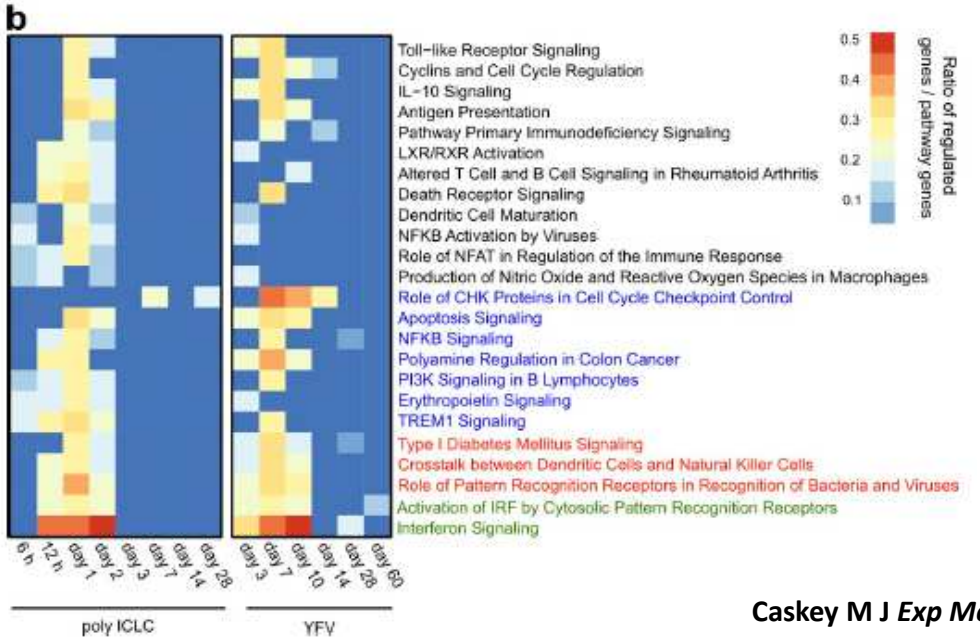
Our immune systems have evolved to recognize them:

Obeid, *Sem. Oncol,* 2015

Poly ICLC and CPG DNA are highly effective vaccine adjuvants

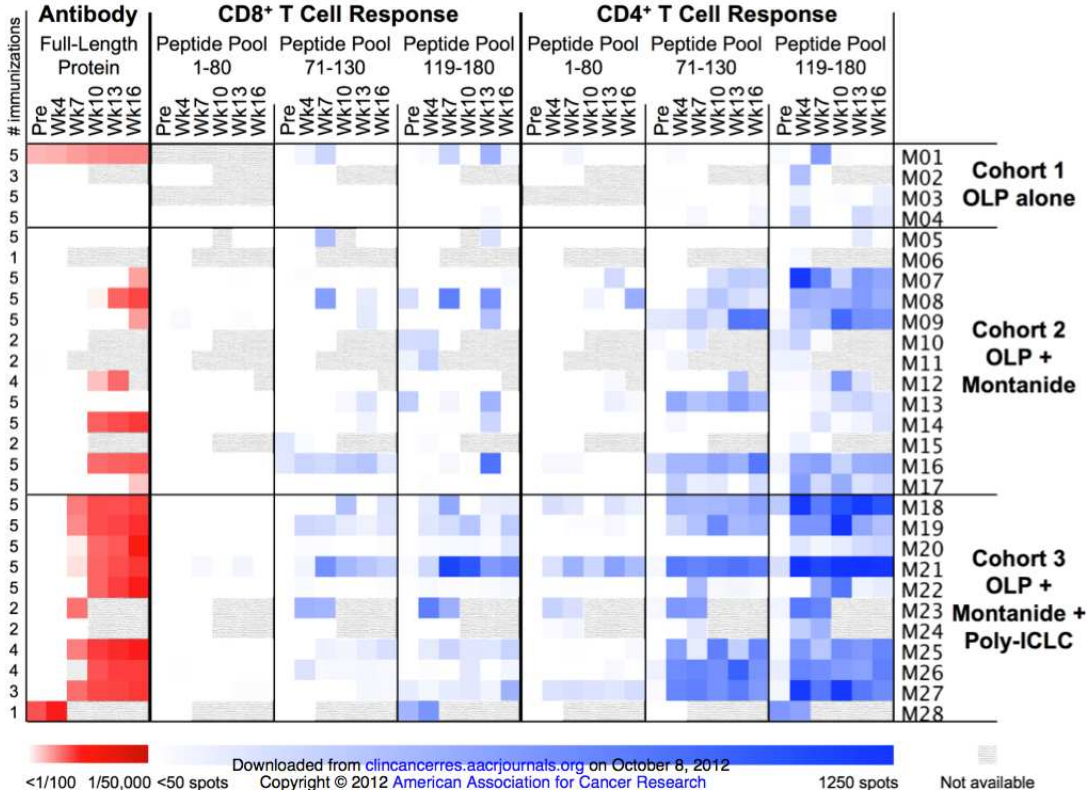
- Nucleic acid ligands of TLR/RLRs are effective adjuvants
  - CpG DNA is difficult to obtain for trials
  - dsRNA stimulates several key pathogen sensors

- Stabilization of pIC in a complex with carboxymethylcellulose, poly-lysine and pIC



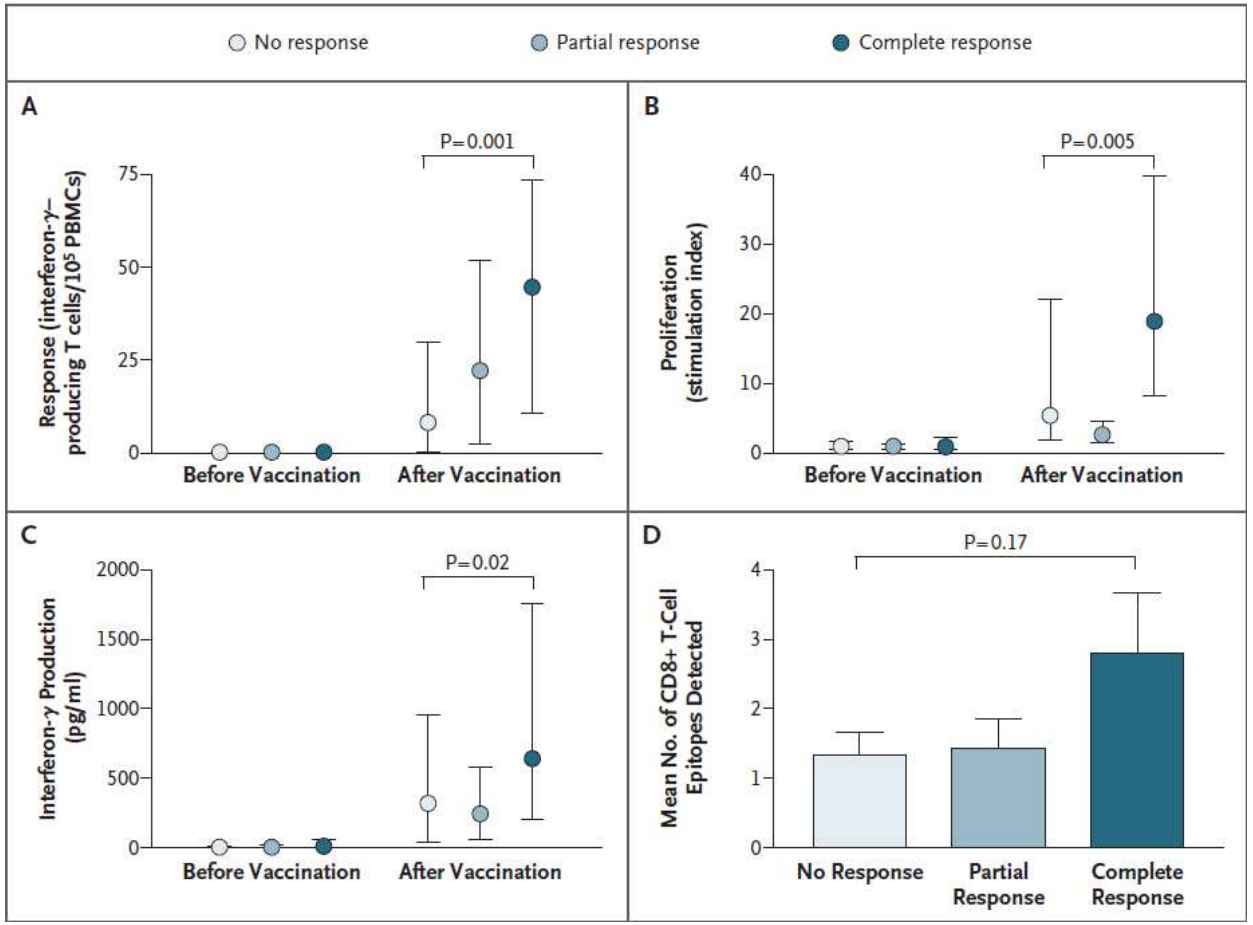
Caskey M J *Exp Med. 2011*

Poly ICLC is safe in humans and effective for mounting immune responses



Sabbatini *Clin Can Res 2012*

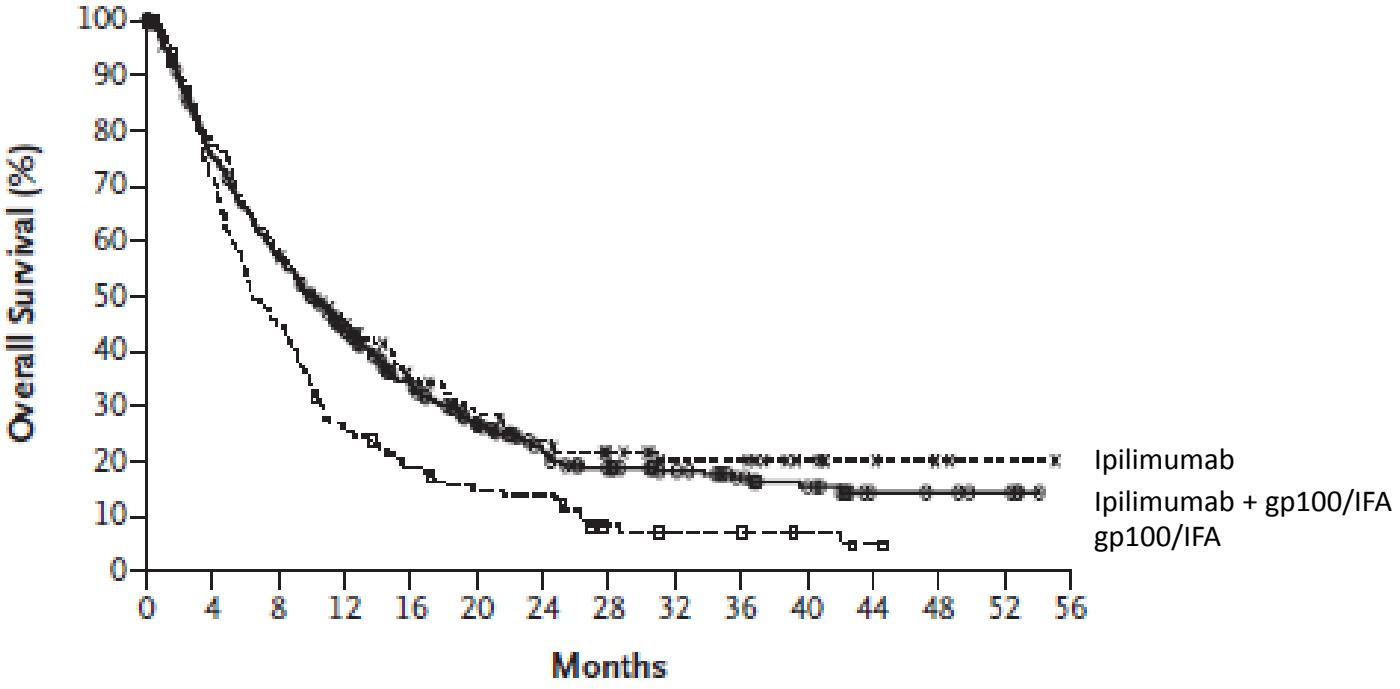
Vaccination with SLP against HPV-16 Oncoproteins for Vulvar Intraepithelial Neoplasia



Kenter, *NEJM*, 2009

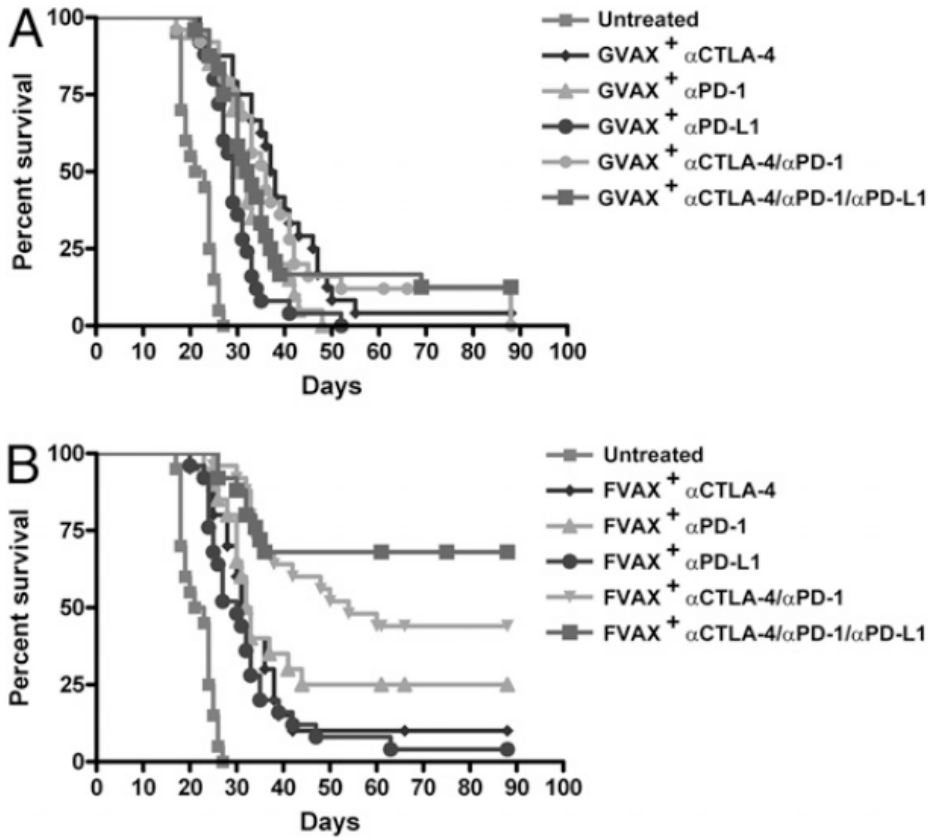
Immune checkpoint blockade plus vaccine?

Ipilimumab plus peptide vaccine gp100



Hodi NEJM 2010

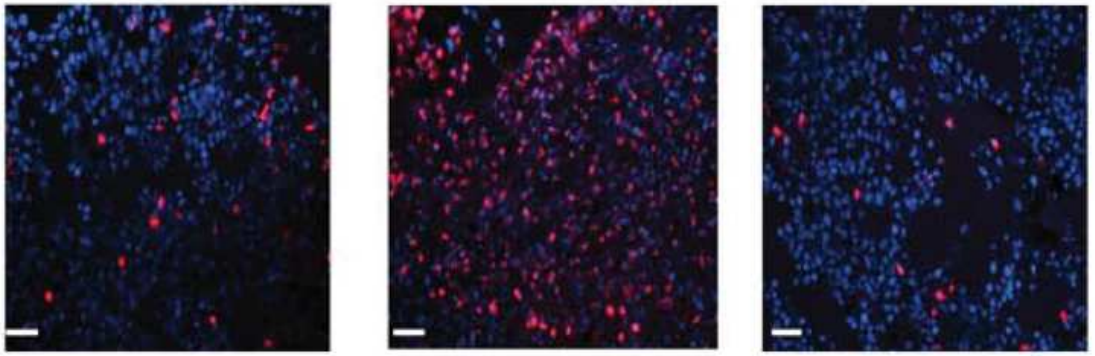
Blockade of CTLA-4, PD-1, and PD-L1 Each Promotes Rejection of B16 melanoma and is additive when used in combination



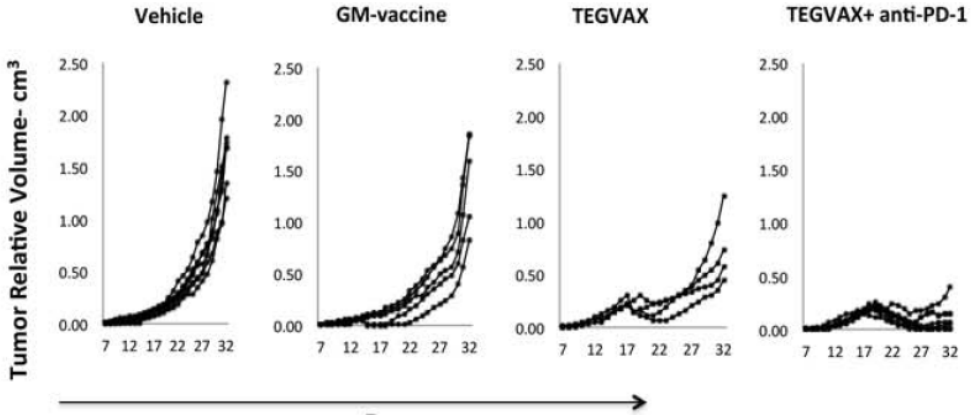
Curran MA *PNAS* 2010

PD-1 blockade cooperates with cancer vaccine TEGVAX to elicit regression of established tumors

PD-L1 expression



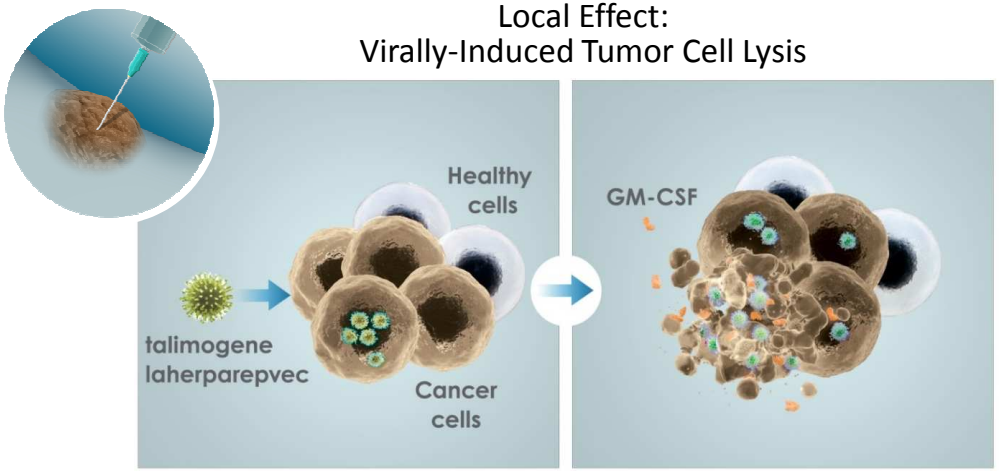
GM-vaccine TEGVAX TEGVAX + anti-IFN-γ



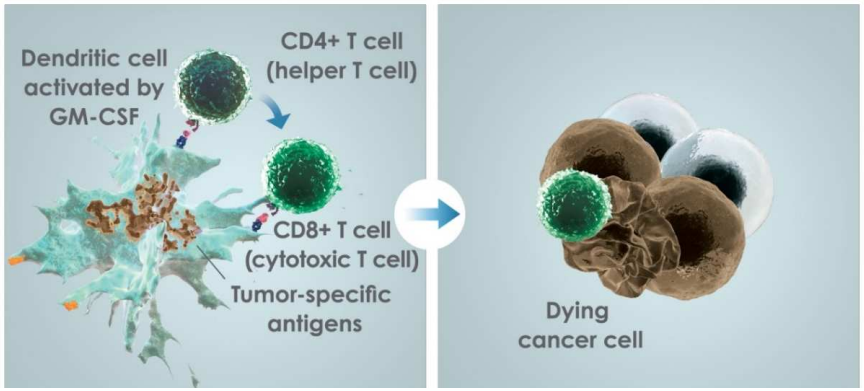
Fu, *Cancer Res*, 2014

T-VEC: An HSV-1-Derived Oncolytic Immunotherapy Designed to Produce Local and Systemic Effects

Local Effect:
Virally-Induced Tumor Cell Lysis



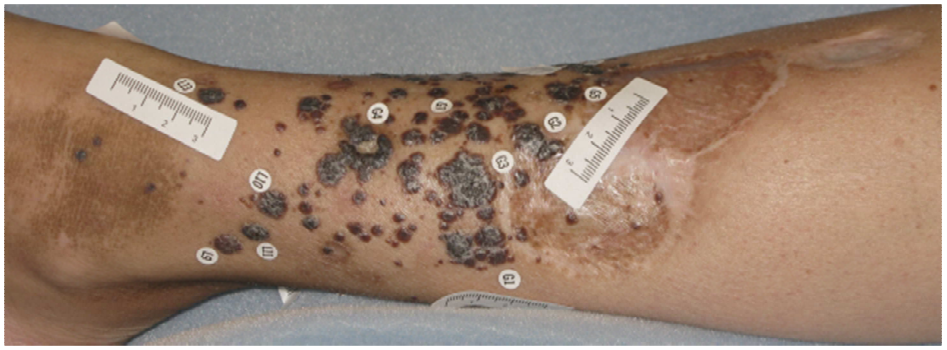
Systemic Effect:
Tumor-Specific Immune Response



Kaufman et al. ASCO 2014, J Clin Oncol 31, 2013 (suppl; abstr LBA9008)

T-VEC Responses in Injected And Uninjected Lesions

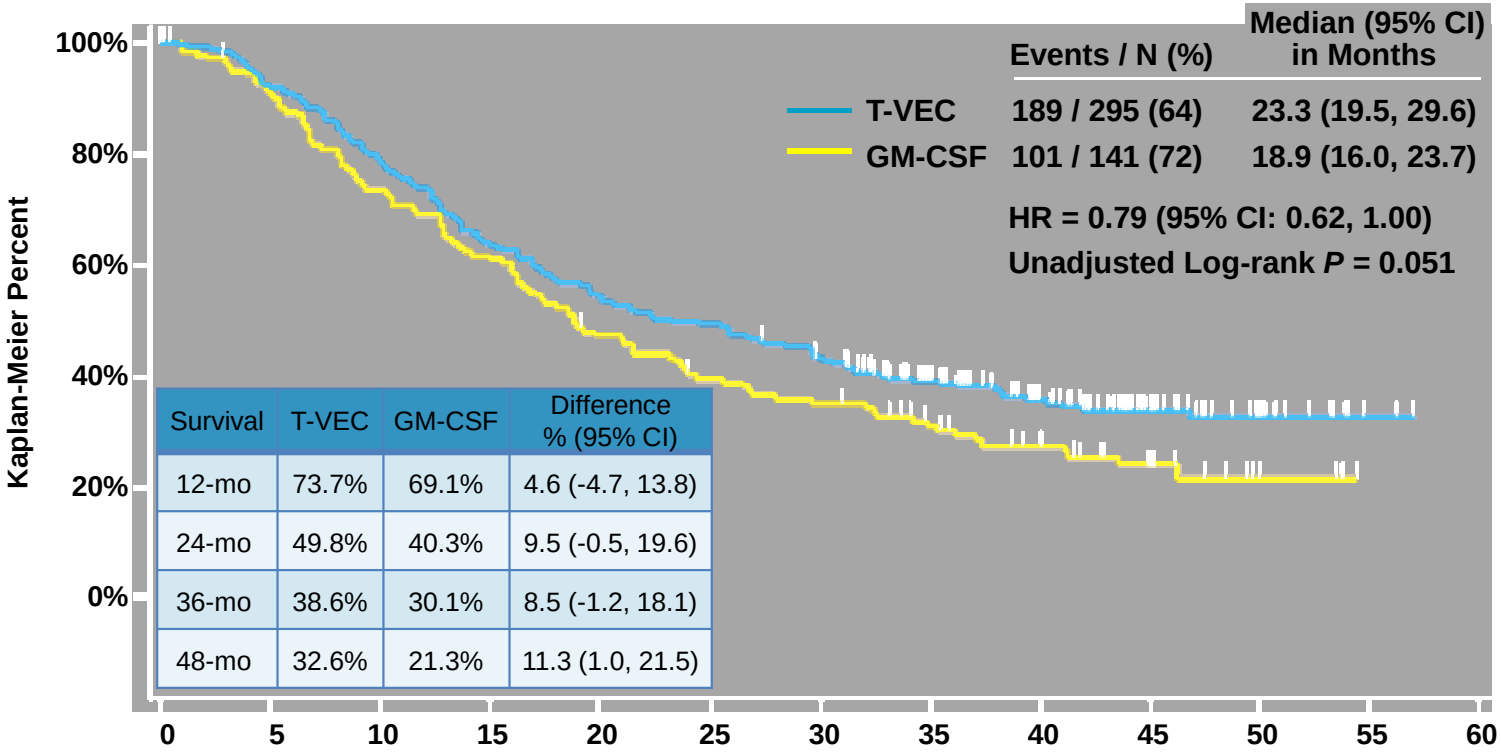
Cycle 1



Cycle 13

Kaufman et al. ASCO 2014, J Clin Oncol 31, 2013 (suppl; abstr LBA9008)

Primary Overall Survival



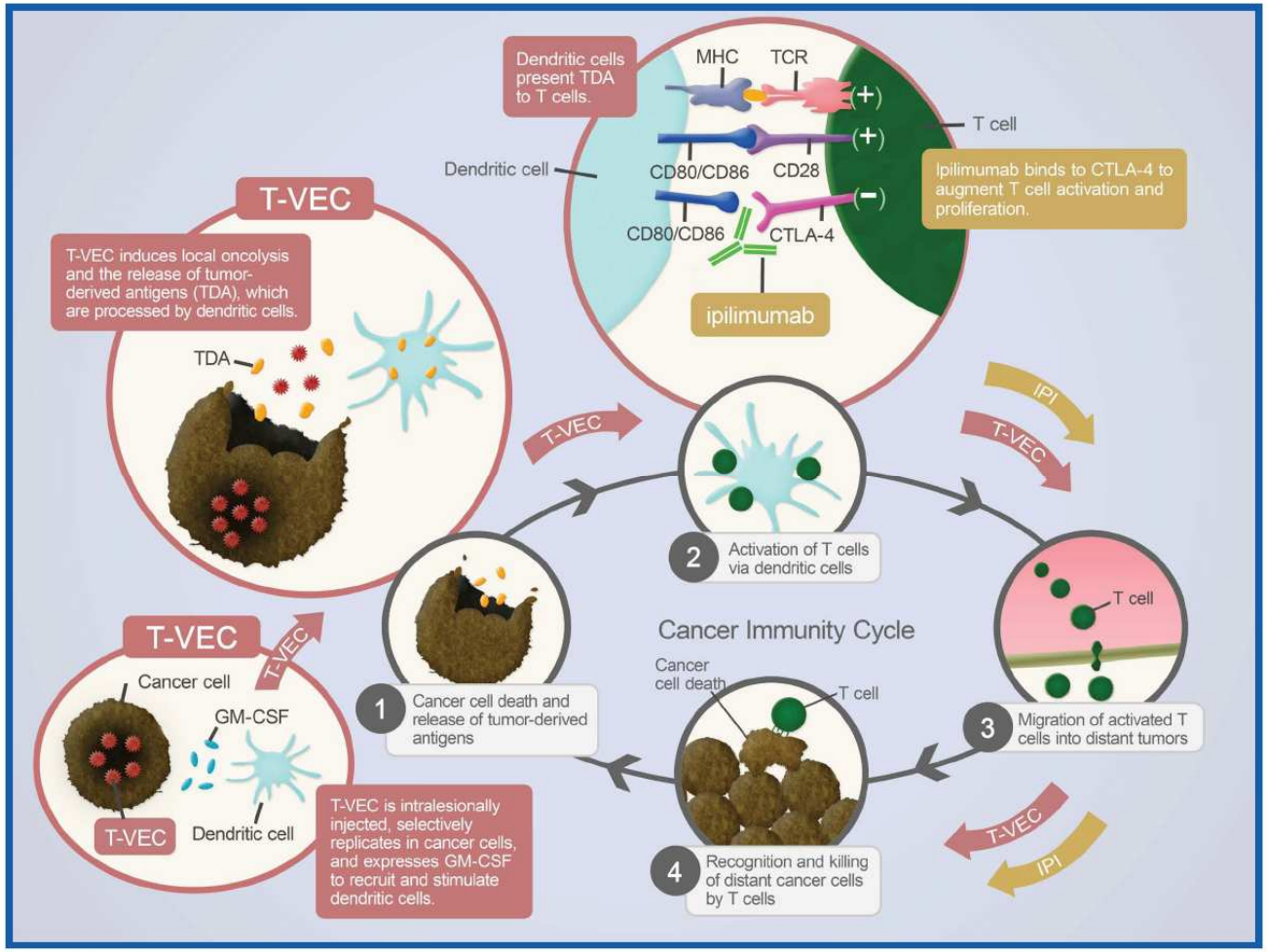
Survival	T-VEC	GM-CSF	Difference % (95% CI)
12-mo	73.7%	69.1%	4.6 (-4.7, 13.8)
24-mo	49.8%	40.3%	9.5 (-0.5, 19.6)
36-mo	38.6%	30.1%	8.5 (-1.2, 18.1)
48-mo	32.6%	21.3%	11.3 (1.0, 21.5)

Patients at risk:

T-VEC	295	269	230	187	159	145	125	95	66	36	16	2	0
GM-CSF	141	124	100	83	63	52	46	36	27	15	5	0	0

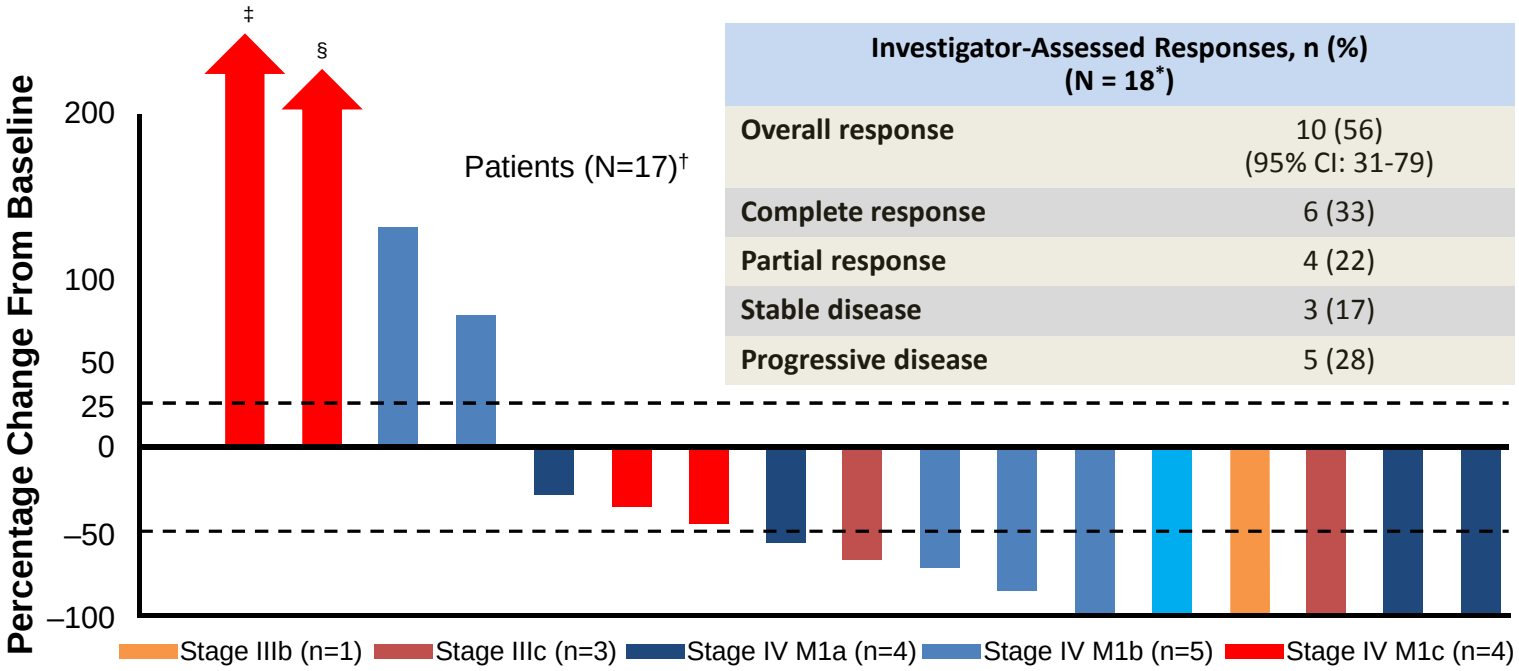
Kaufman et al. ASCO 2014, J Clin Oncol 31, 2013 (suppl; abstr LBA9008)

T-VEC to augment immune-checkpoint blockade?



Puzanov I, et al. ASCO 2014. J Clin Oncol 32:5s, 2014 (suppl; abstr 9029^)

T-Vec + Ipi in Unresected Stage IIIB-IV Melanoma: Max Change in Tumor Burden



Investigator-Assessed Responses, n (%) (N = 18*)	
Overall response	10 (56) (95% CI: 31-79)
Complete response	6 (33)
Partial response	4 (22)
Stable disease	3 (17)
Progressive disease	5 (28)

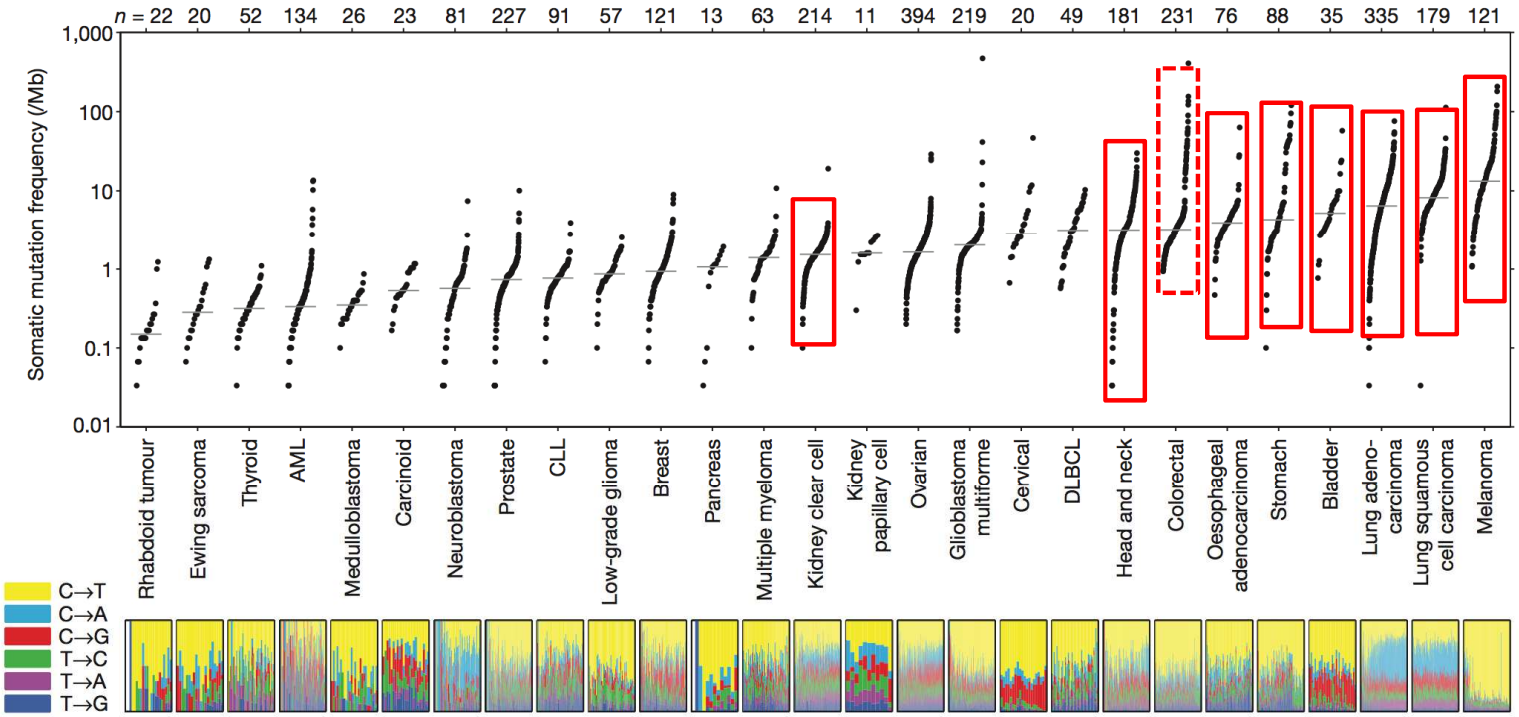
*Only patients who received both T-Vec and ipilimumab. CR, CRu, and PD included.
† One patient with PD not shown in the plot because tumor burden could not be accurately calculated (missing post-baseline data)
‡ Percentage change from baseline: 538
§ Percentage change from baseline: 265

Puzanov I, et al. ASCO 2014. J Clin Oncol 32:5s, 2014 (suppl; abstr 9029^)

Examples for Novel Approaches

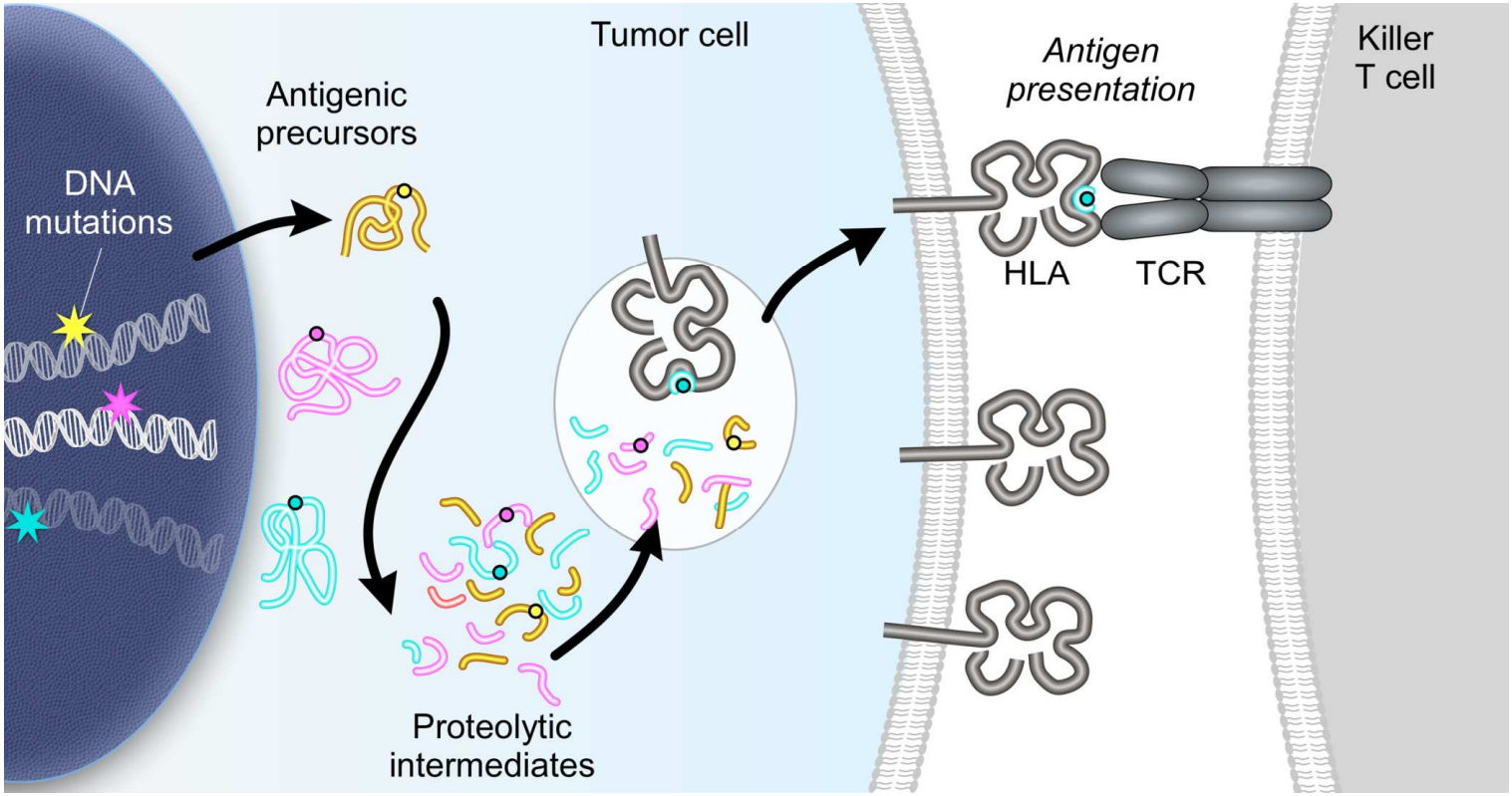
- Neoantigens
- Scaffolds

DNA sequencing across cancers (n= >3000)

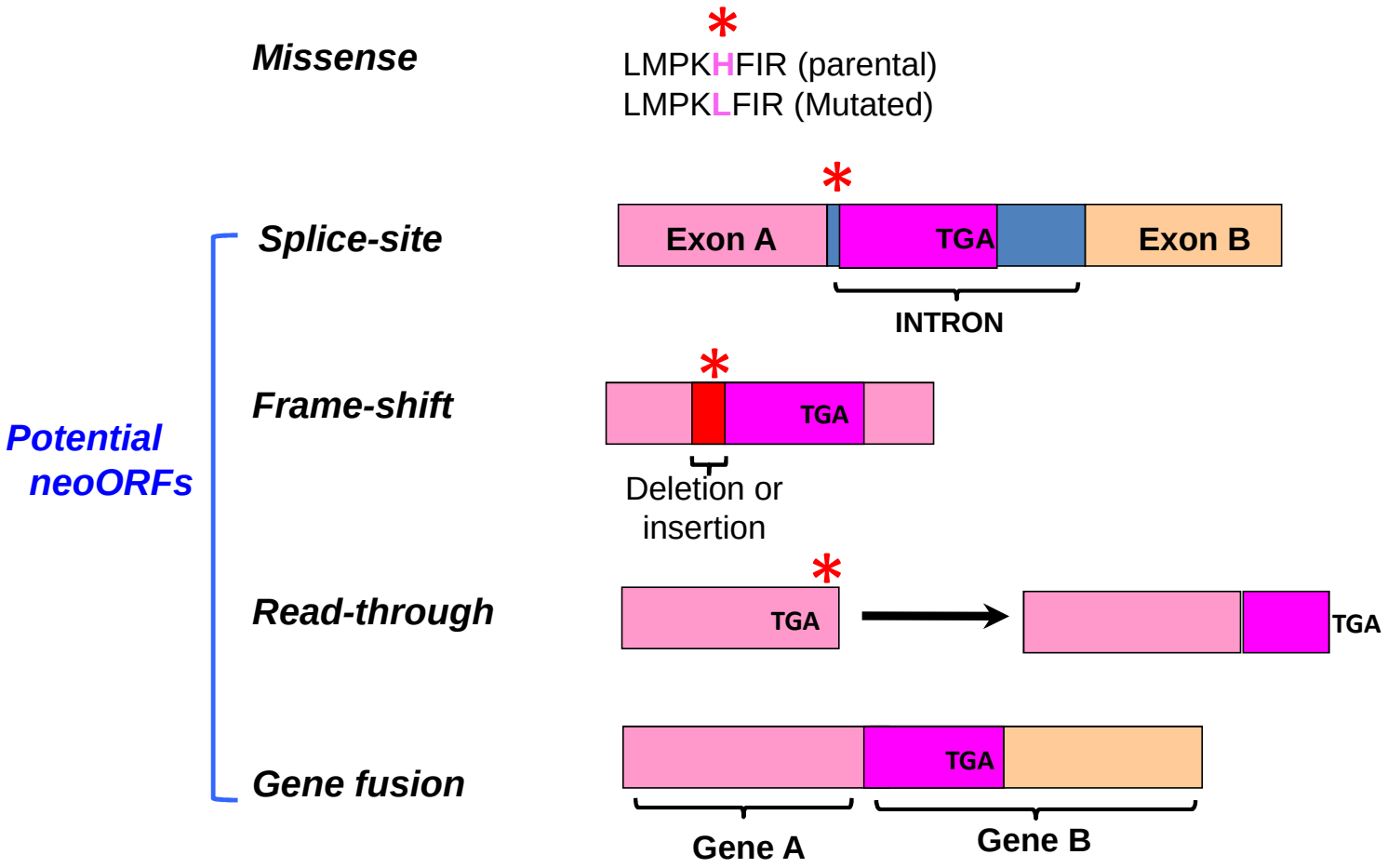


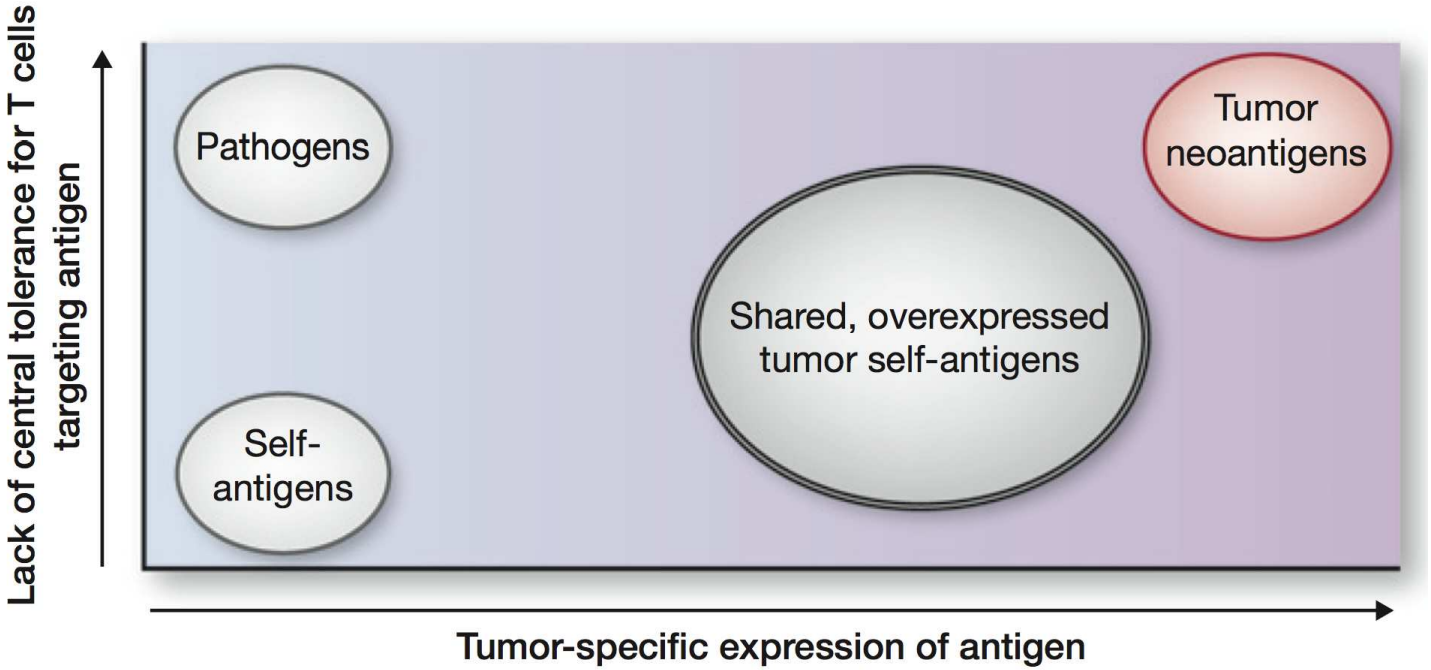
Lawrence MS *Nature* 2013

Somatic mutations have the potential to generate neoantigens



Classes of mutations generate potential tumor neoepitopes





Hacohen et al, Ed Fritsch, *Cancer Immunol Res* 2013

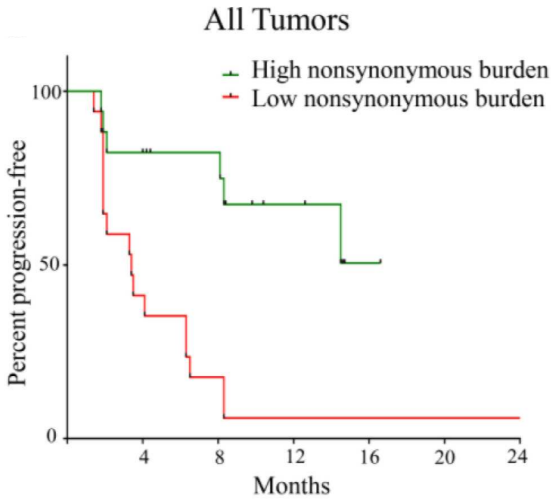
A critical role of neoantigens in the immune control of tumors

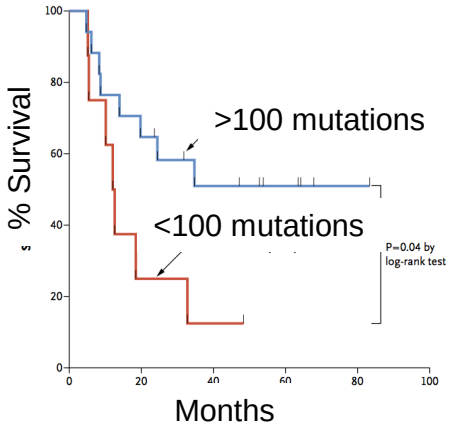
- Neoantigens represent dominant targets in tumor-infiltrating lymphocyte (TIL) populations in patients benefiting from adoptive therapy
- Overall survival improved in patients predicted to have at least one immunogenic neoantigen epitope
- Widespread detection of spontaneously occurring neoantigen-specific T cells
- Checkpoint blockade therapy has revealed neoantigen-specific responses

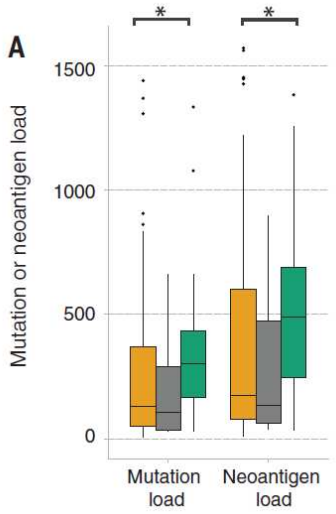
Mutational load correlates with response to αPD1/αPDL1 and ipilimumab

Anti PD1/PDL1

Anti-CTLA-4





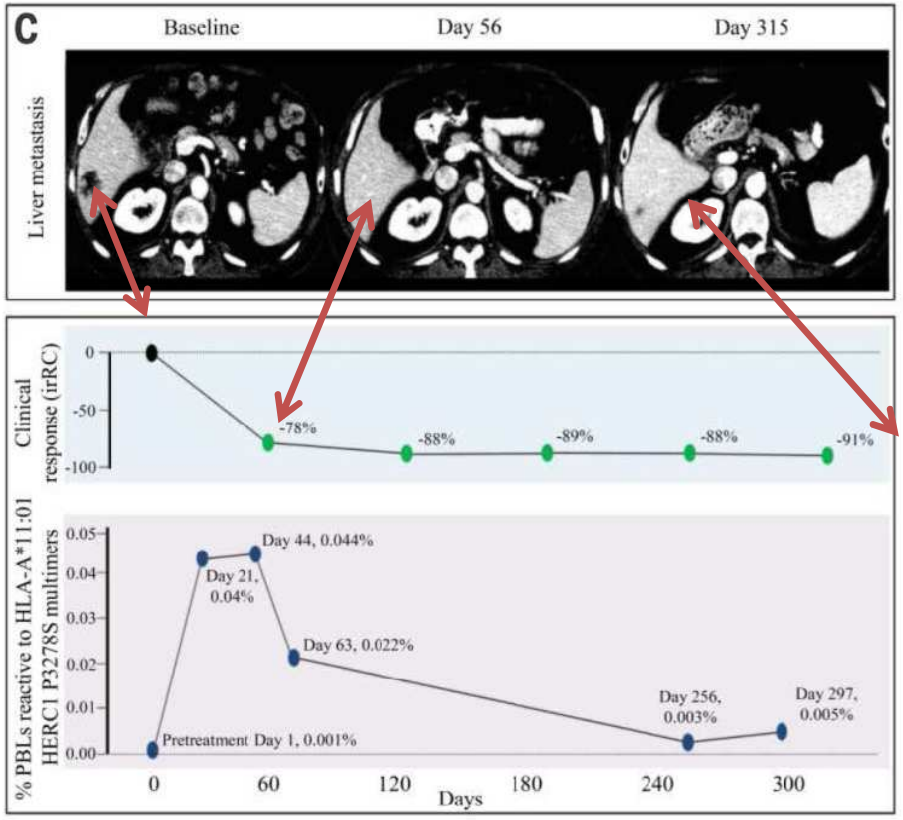


Rivzi et al. Science 2015

Snyder *et al. NEJM* 2014

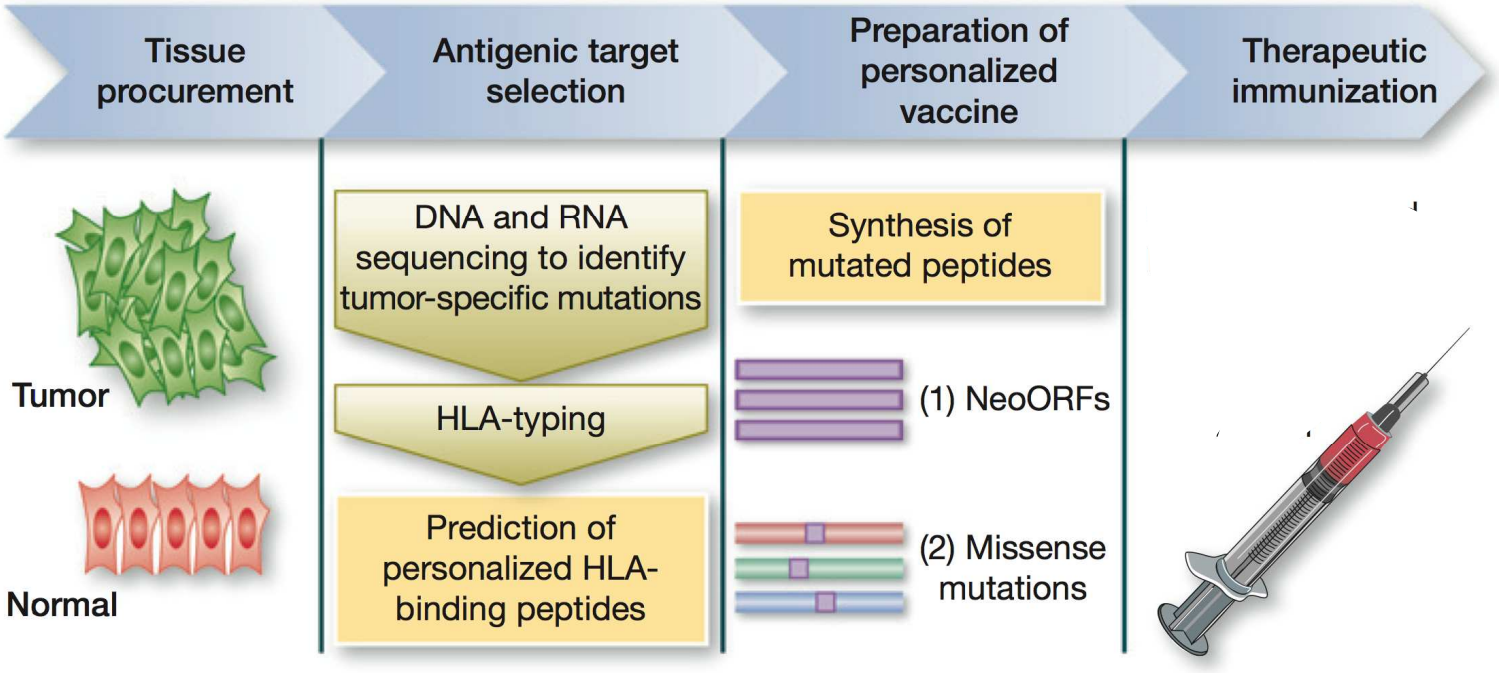
Van Allen et al. Science 2015

Checkpoint blockade therapy induces neoantigen responses, which parallel tumor regression



Rizvi et al, *Science* 2015

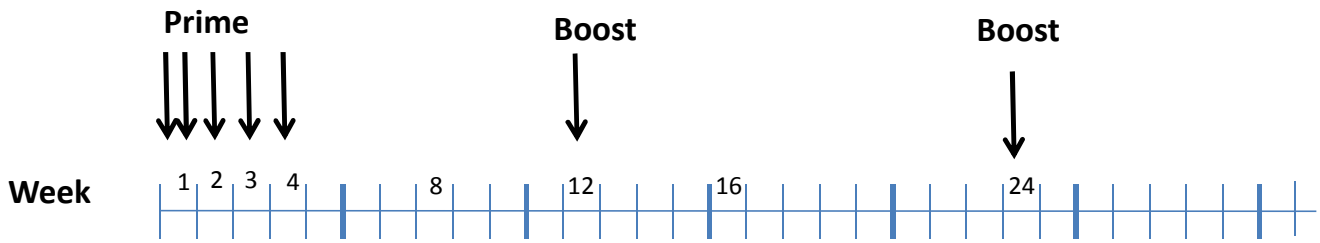
Developing a personalized cancer vaccine based on multiple coding mutations unique to each pt tumor



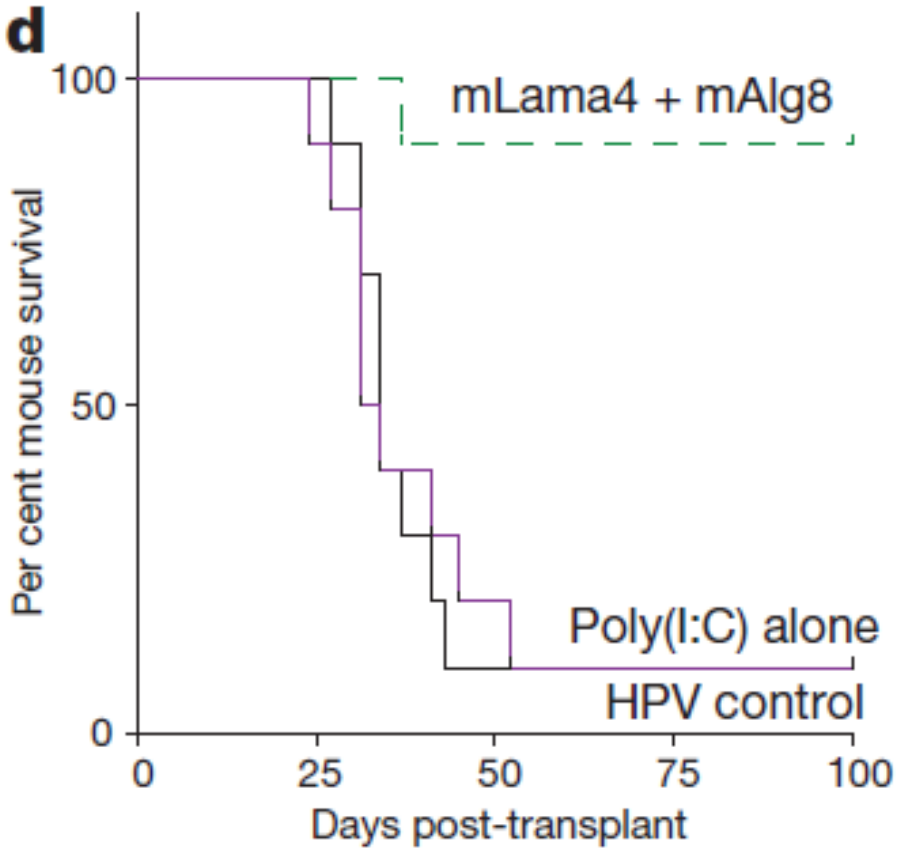
Hacohen et al, *Cancer Immunol Res 2013*

A Phase I Study with a Personalized NeoAntigen Cancer Vaccine in High Risk Melanoma

IND Sponsor and PI: Patrick A. Ott

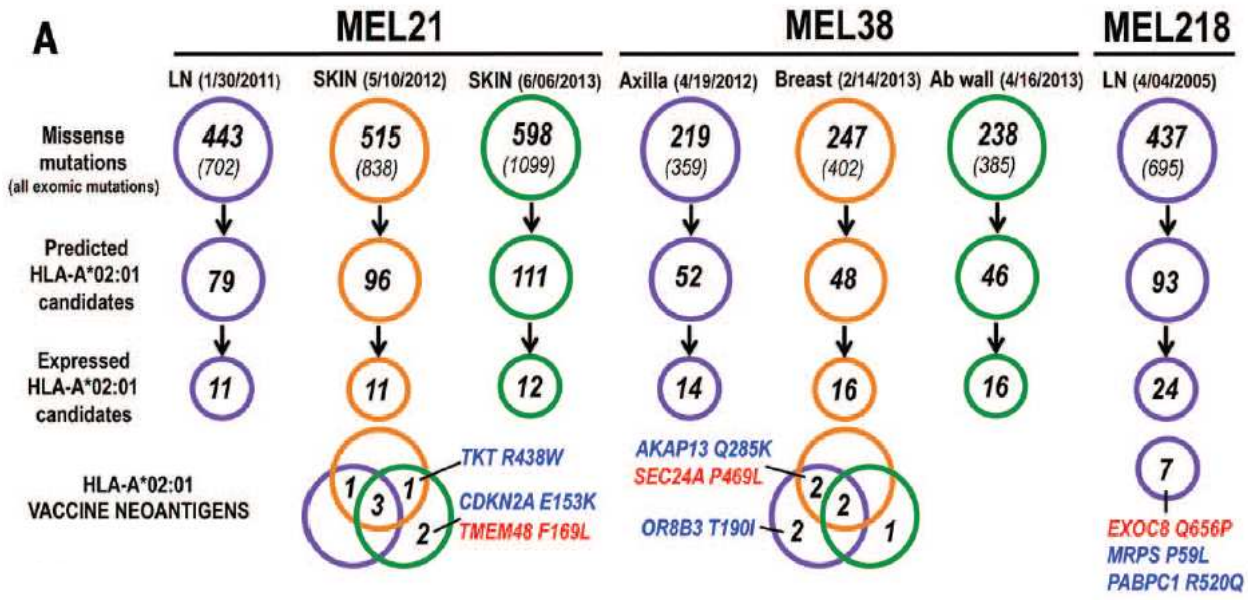


Checkpoint blockade targets tumor neoantigens in an MCA sarcoma mouse model



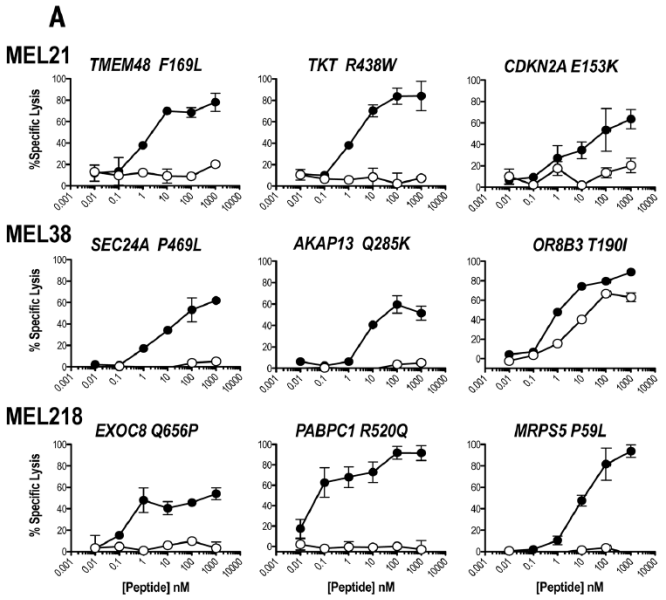
Gubin et al. N*ature* 2014

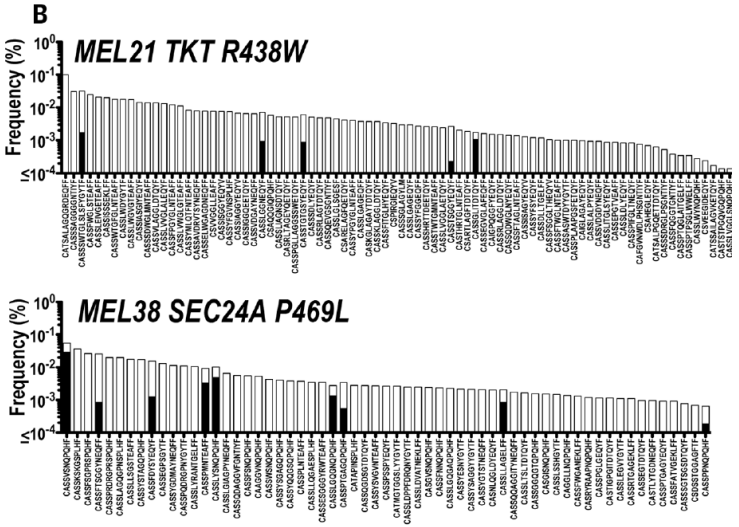
Dendritic cell vaccine increases the breath and diversity of melanoma neoantigen specific T cells



Carreno et al, *Science,* 2015

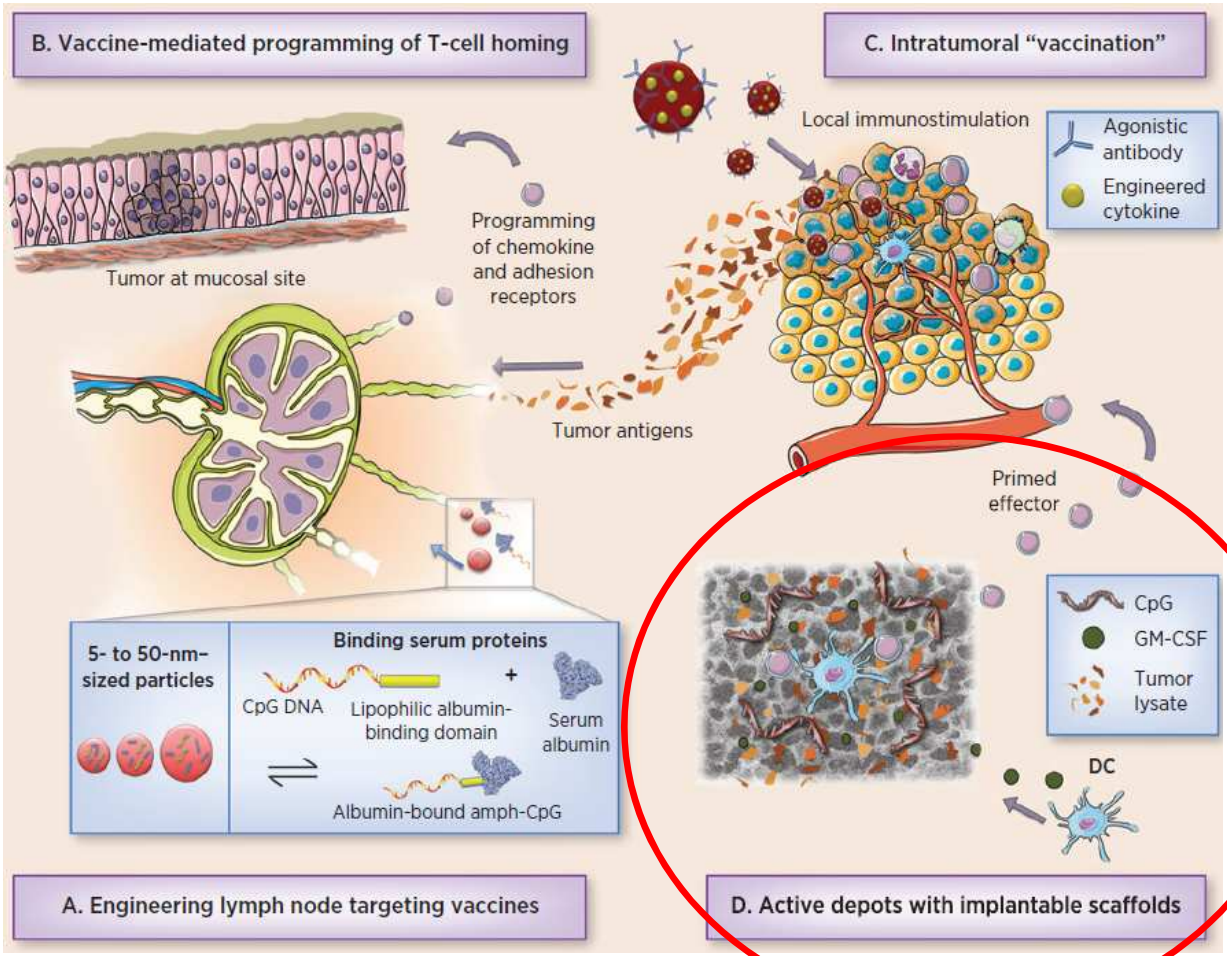
Dendritic cell vaccine increases the breath and diversity of melanoma neoantigen specific T cells





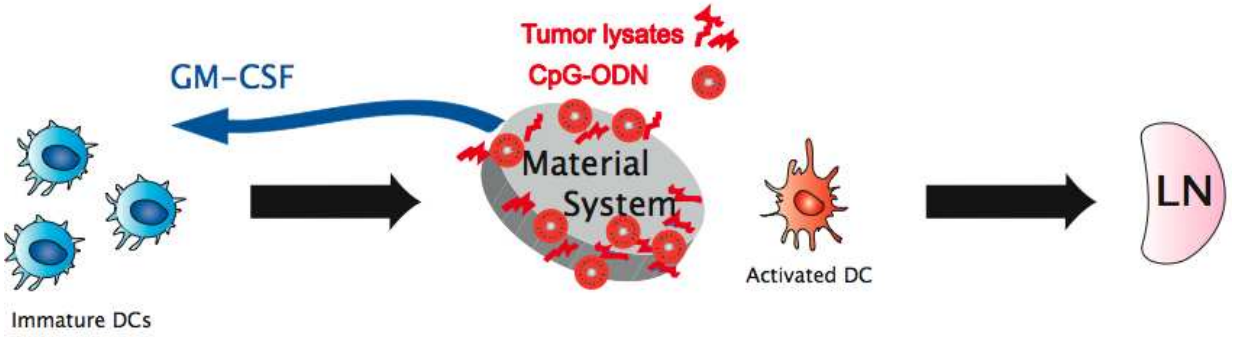
Carreno et al, *Science,* 2015

Strategies for engineering more effective cancer vaccines



Mehta et al, CIR, 2015

Biodegradable Scaffolds - Hypothesis

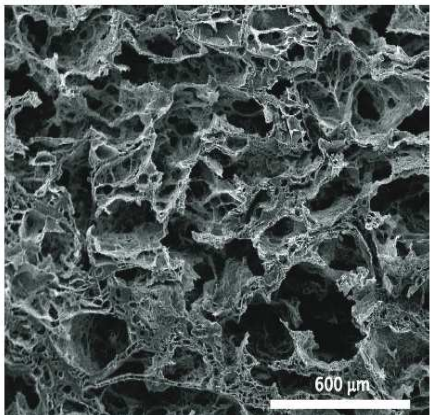


- GM-CSF recruits and activates dendritic cells to stimulate T effectors
- CpG triggers TLR9 signaling → DC activation, production of type I interferons, cytokines, and chemokines.
- Necrotic tumor cell lysate provides the target antigens for vaccine response

Engineered polymer (PLGA) scaffolds

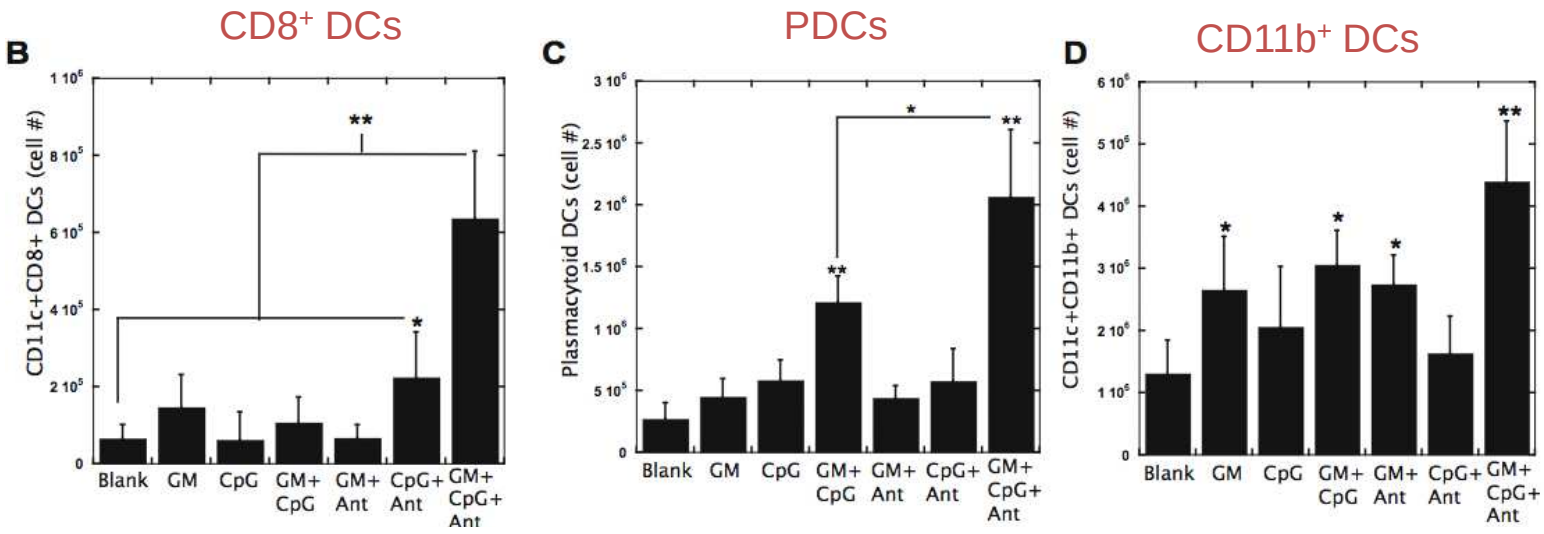
2 mm thickness

8 mm diameter



Wyss Institute for
Biologically Inspired Engineering

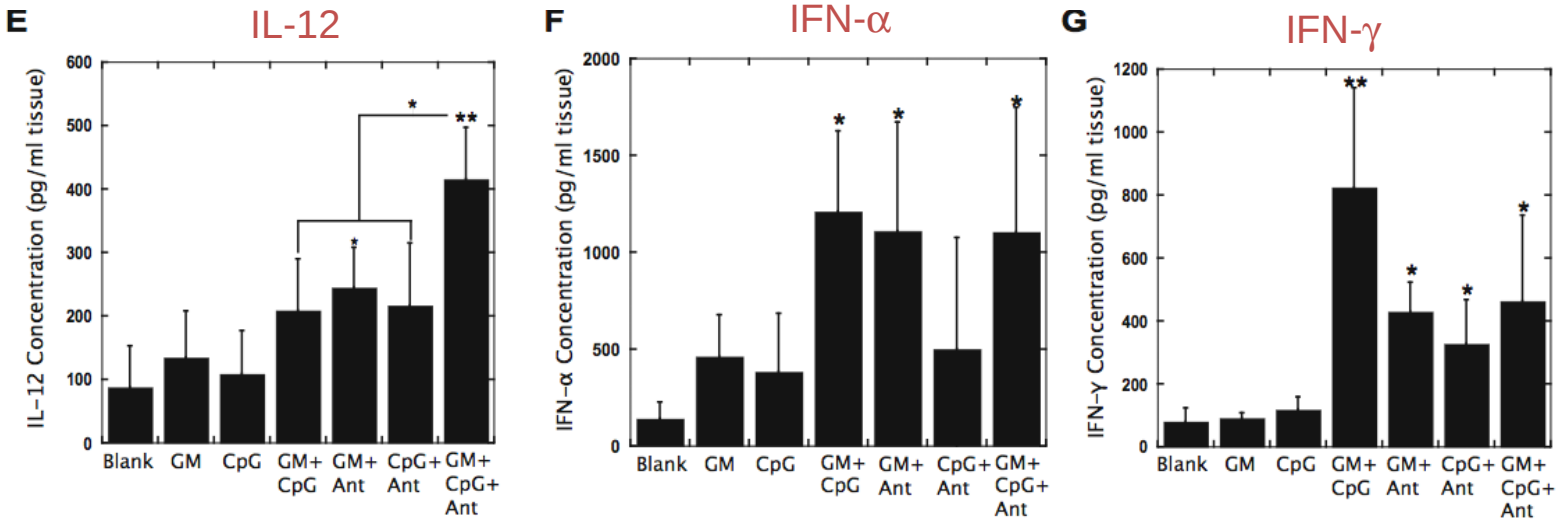
Necrotic B16 lysates + GM-CSF + CpG stimulate a broad dendritic cell response



Day 10

Ali *Sci Transl Med* 2009

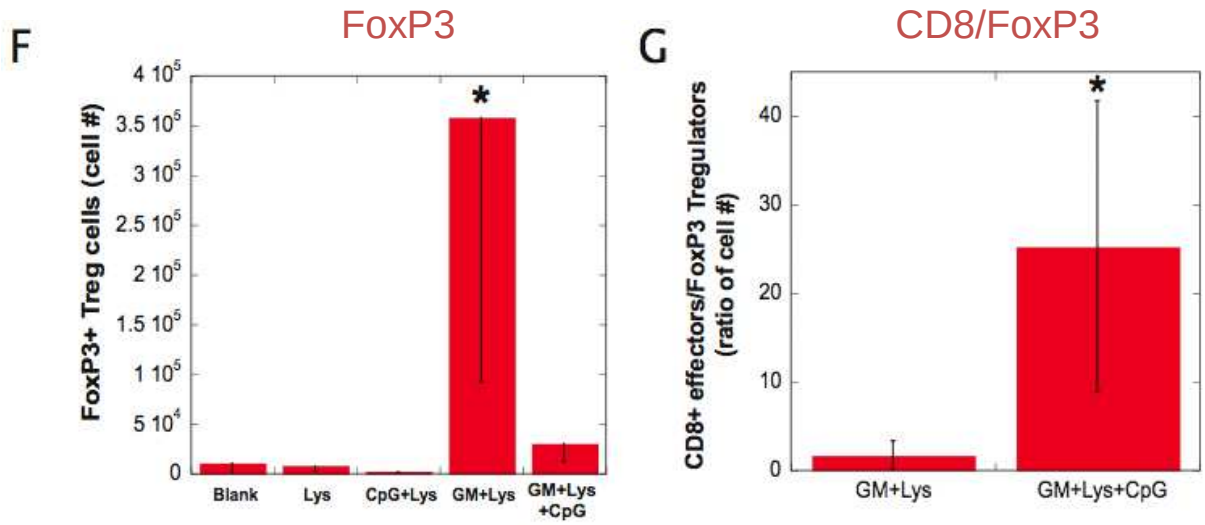
Scaffold delivered GM-CSF/CpG/B16 lysates elicit Th1 promoting cytokines



Day 10

Ali Sci Transl Medicine 2009

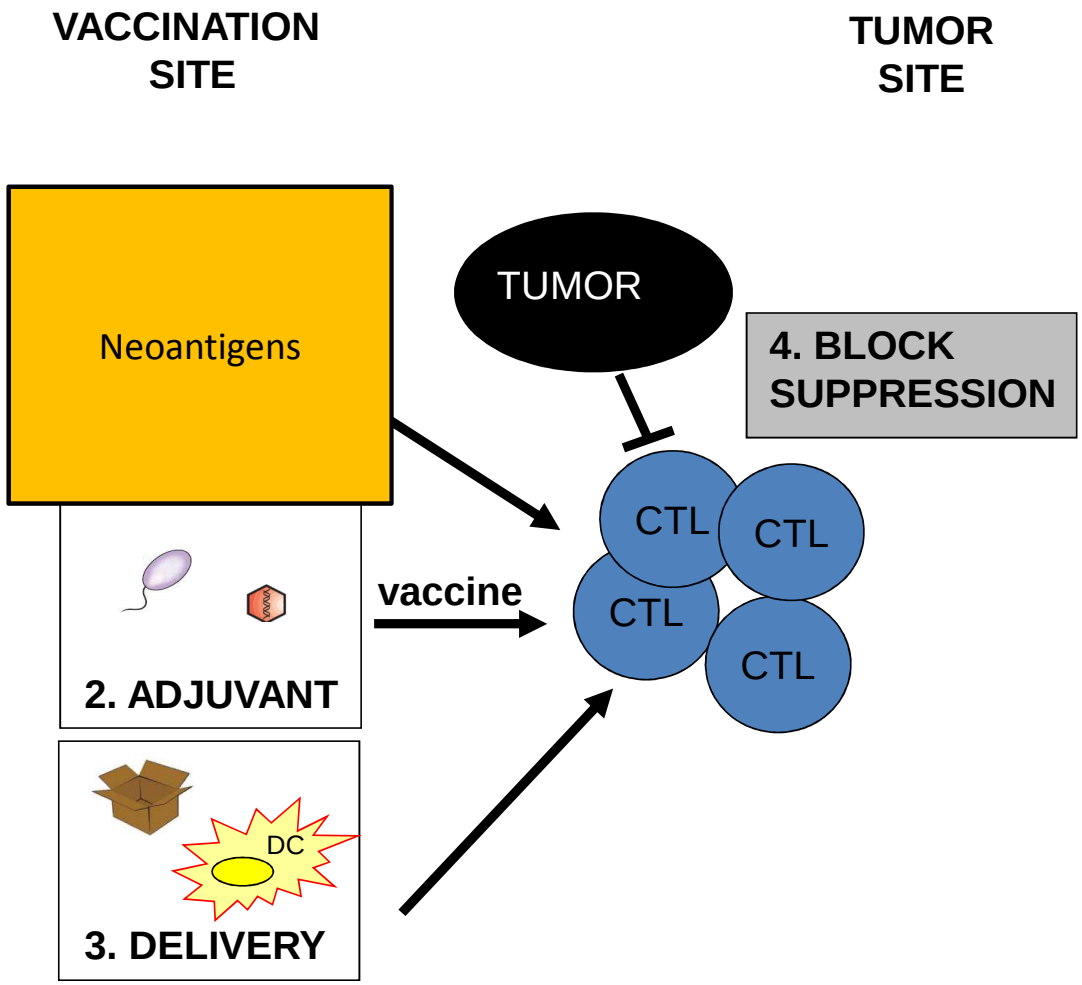
Scaffold delivered GM-CSF/CpG/B16 lysates stimulate a high Teff/Treg ratio

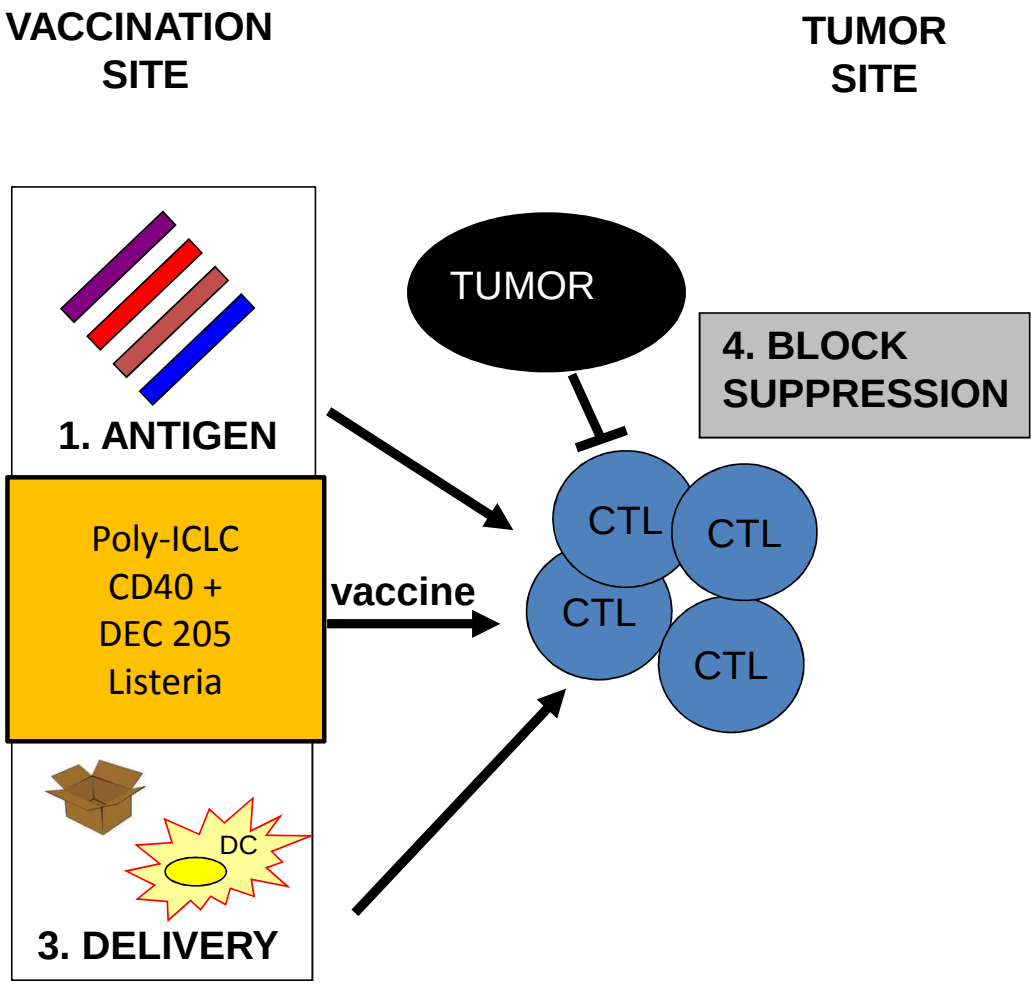


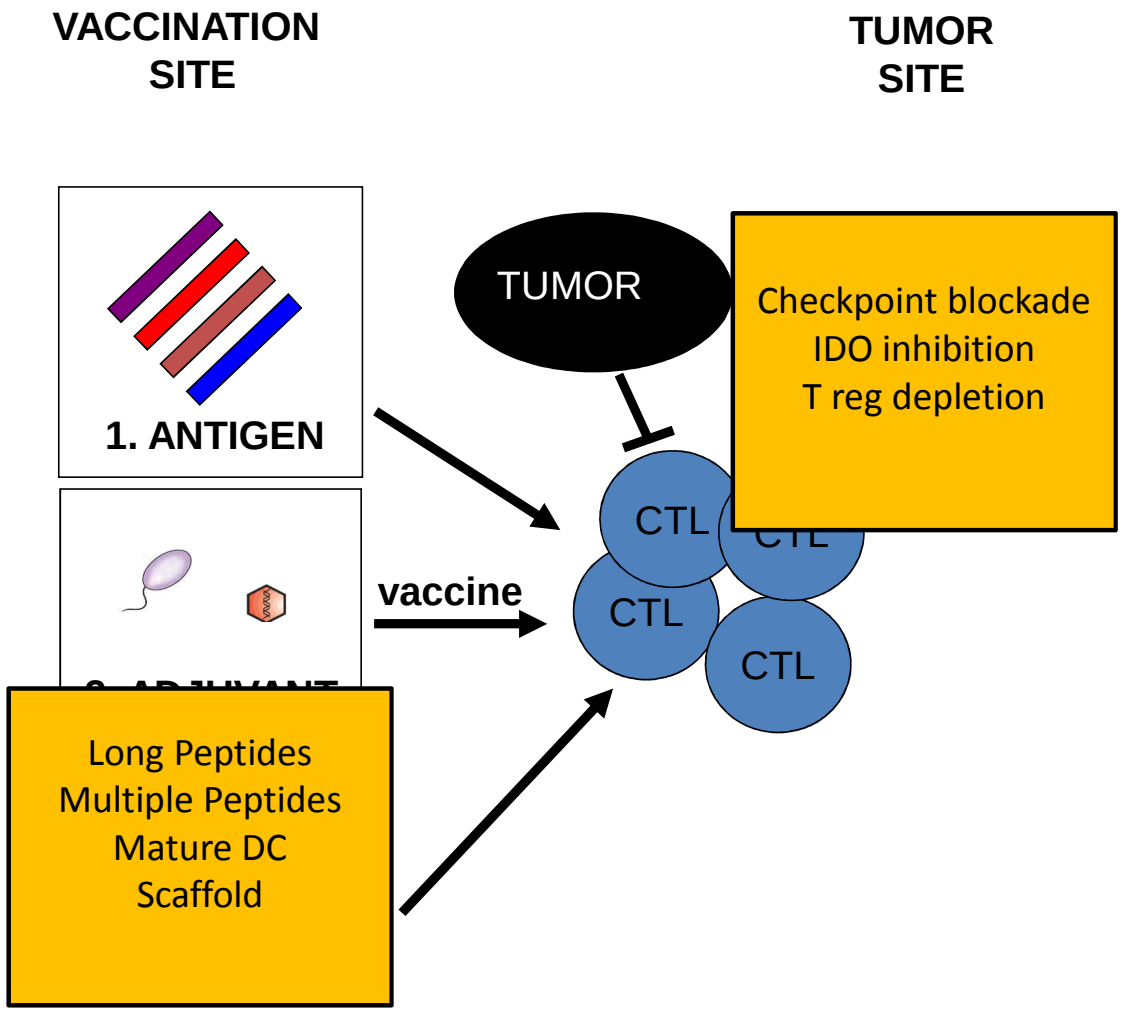
Day 12 implantation sites

Ali *Sci Transl Med* 2009

A Phase I Trial of a Dendritic Cell Activating Scaffold Vaccine (WDVAX) Incorporating Autologous Melanoma Cell Lysate in Metastatic Melanoma Patients


VACCINATION SITE
TUMOR SITE
Neoantigens
TUMOR
4. BLOCK SUPPRESSION
CTL
CTL
CTL
CTL
vaccine
2. ADJUVANT
DC
3. DELIVERY


VACCINATION SITE
TUMOR SITE
1. ANTIGEN
Poly-ICLC
CD40 +
DEC 205
Listeria
vaccine
DC
3. DELIVERY
TUMOR
4. BLOCK SUPPRESSION
CTL
CTL
CTL
CTL


VACCINATION SITE
TUMOR SITE
1. ANTIGEN
TUMOR
Checkpoint blockade
IDO inhibition
T reg depletion
vaccine
CTL
CTL
CTL
Long Peptides
Multiple Peptides
Mature DC
Scaffold