Cancer Immunotherapy: Active Immunization Approaches

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Society for Immunotherapy of Cancer

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- There will be discussion about the use of products for non-FDA approved indications in this presentation.

Goals

1. To understand the development of active immunotherapy of cancer

2. To be aware of limitations associated with active immunization approaches for cancer care

3. To review the outcomes of various active immunization strategies for the treatment of cancer

Categories of Immunotherapy

	Active	Passive
Tumor Specific	Vaccines	Monoclonal Antibodies
Tumor Non-Specific	Immunologic Checkpoint Inhibitors	Cytokines

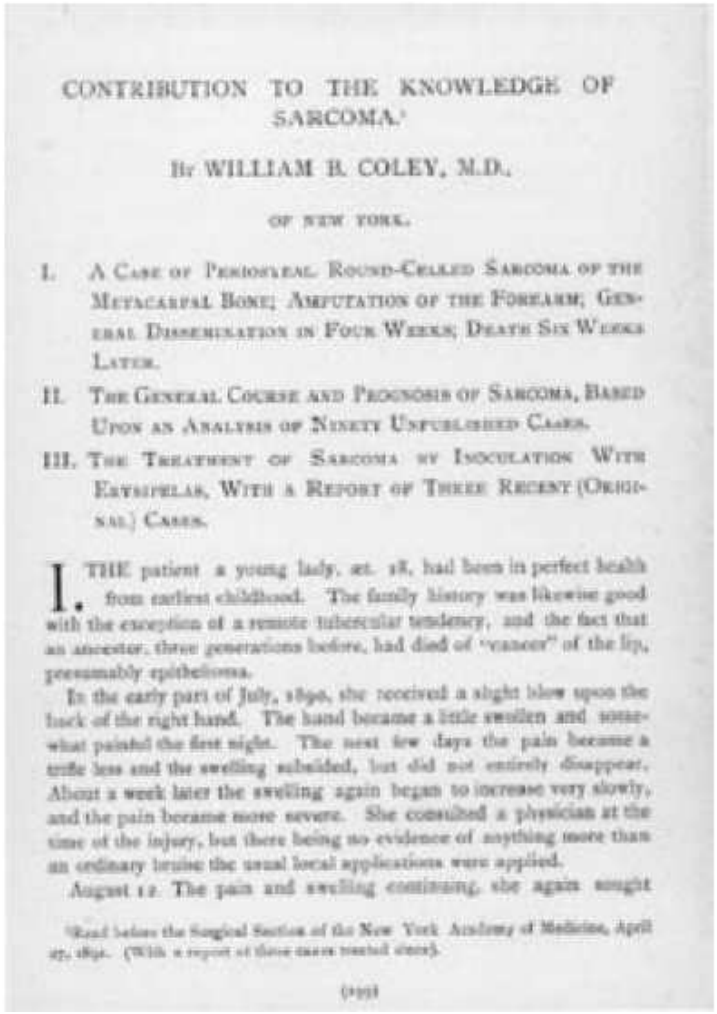
Active Immunotherapy: Uses the patient's own immune system for antitumor effects

- **Cancer Prevention**
- **Cancer Therapy**

First Non-Specific Cancer Vaccine: Coley's Toxin
(Heat-killed *Streptococci* & *Serratia marcescens)*

William B. Coley
(1862 – 1936)

Chief, Bone Sarcoma Unit
Memorial Hospital
New York



CONTRIBUTION TO THE KNOWLEDGE OF SARCOMA.[1]

By WILLIAM B. COLEY, M.D.,

OF NEW YORK.

I. A Case of Periosteal Round-Celled Sarcoma of the Metacarpal Bone; Amputation of the Forearm; General Dissemination in Four Weeks; Death Six Weeks Later.

II. The General Course and Prognosis of Sarcoma, Based Upon an Analysis of Ninety Unpublished Cases.

III. The Treatment of Sarcoma by Inoculation With Erysipelas, With a Report of Three Recent (Original) Cases.

I. THE patient a young lady, æt. 18, had been in perfect health from earliest childhood. The family history was likewise good with the exception of a remote tubercular tendency, and the fact that an ancestor, three generations before, had died of "cancer" of the lip, presumably epithelioma.

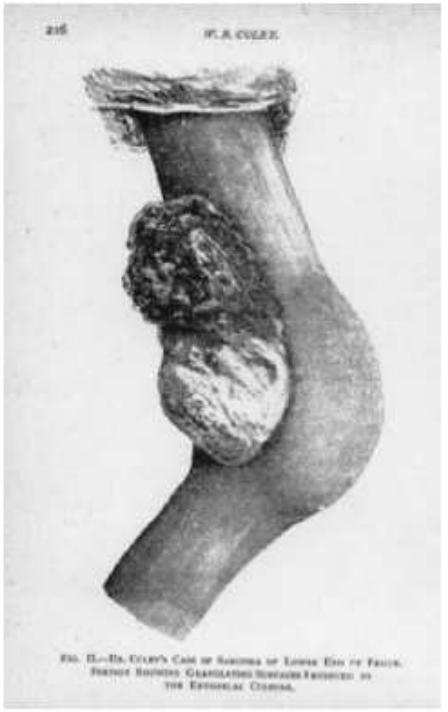
In the early part of July, 1890, she received a slight blow upon the back of the right hand. The hand became a little swollen and somewhat painful the first night. The next few days the pain became a trifle less and the swelling subsided, but did not entirely disappear. About a week later the swelling again began to increase very slowly, and the pain became more severe. She consulted a physician at the time of the injury, but there being no evidence of anything more than an ordinary bruise the usual local applications were applied.

August 12. The pain and swelling continuing, she again sought

[1]Read before the Surgical Section of the New York Academy of Medicine, April 27, 1891. (With a report of three cases treated since).

(199)

Coley WB. *Annals of Surgery* 1891;14:199–200



Coley's First Bone Sarcoma Case

McCarthy EF. *IOWA Orthop J*, 2006

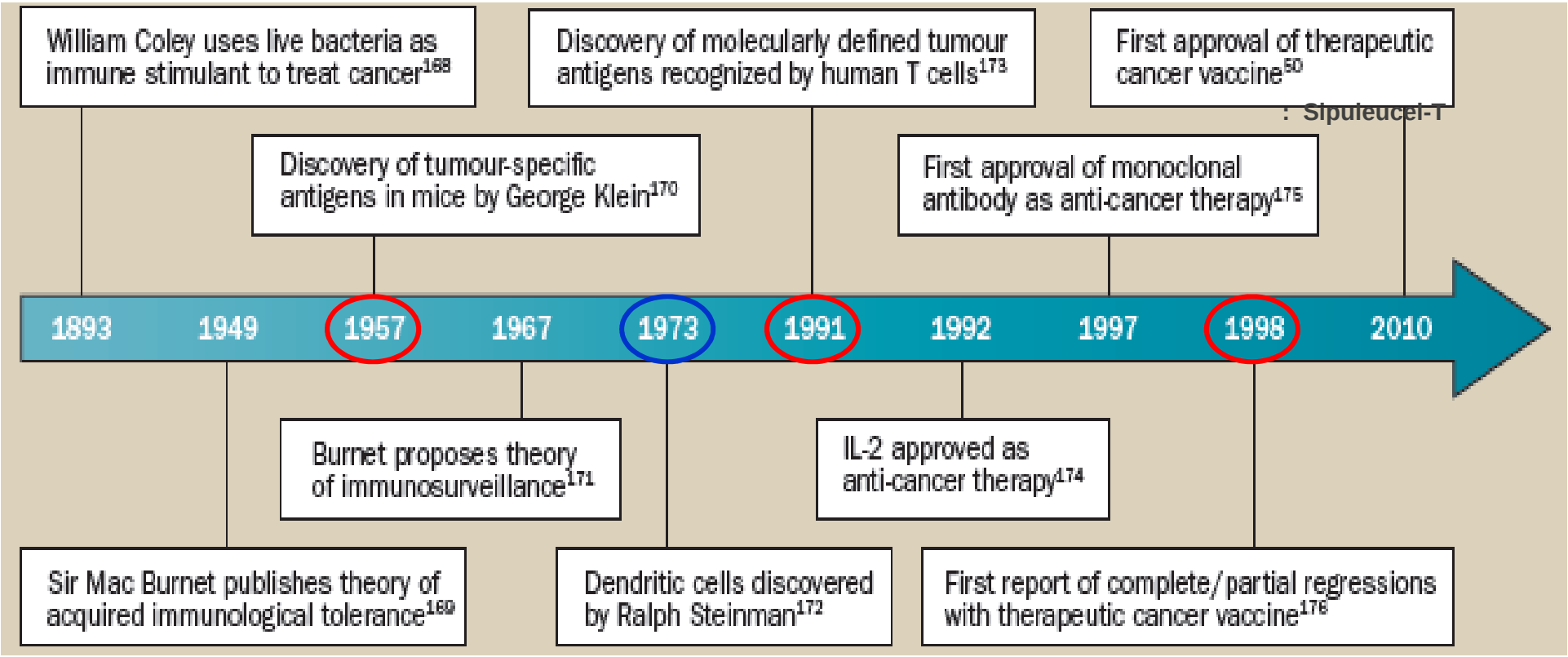
Potential Benefits of Coley's Toxins

End Results of 484 Cases of Malignant Disease with Histologic Confirmation in Which Coley's Toxins Were Used

Type of tumor	Total no. cases	Inoperable		Operable	
		Total	Five year survivals	Total	Five year survivals
Carcinoma	69	45	15	24	21
Malignant melanoma	24	19	4	5	3
Bone sarcoma	205	98	37	107	51
Soft parts sarcoma	123	91	53	32	25
Lymphosarcoma	49	45	24	4	4
Hodgkin's Disease	14	14	1	0	0
Total	484	312	134	172	105

49% success rate

Milestones in Active Immunization



What is a Modern Tumor-Specific Cancer Vaccine?

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

Challenges in Developing a Cancer Vaccine

- Target antigens are different for each tumor, and the profile of those antigens may change with different stages of tumor

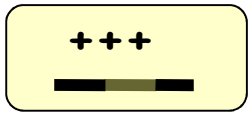
- Although most immunoresponsive tumors "autovaccinate", an effective anti-tumor response is still not achieved because of:
  - Immunosuppressed tumor microenvironment
  - Activation of immunologic checkpoints

Human tumor Ag recognized by T cells

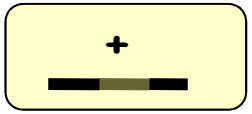
Adapted from P.G. Coulie et al. 1999

1. Viruses

2. Overexpression



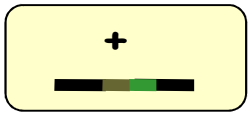
Many tumors



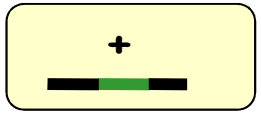
Normal cells

KIT
HER2
HERV
hTERT
P53
Survivin

3. Mutation



Tumors

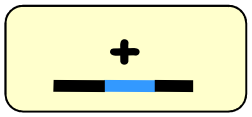


Normal cells

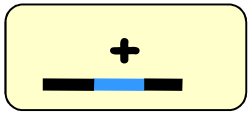
Point mutations
Deletions
Insertions
Frameshifts
Mis-spliced

Unmutated self tumor antigens

4. Differentiation
« Tissue-specific »



Melanomas



Melanocytes

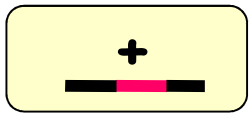
Other normal cells

CEA
PSA
gp100
Melan-A/MART-1
tyrosinase

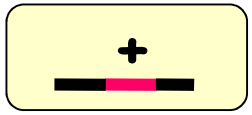
↓

Autoimmunity

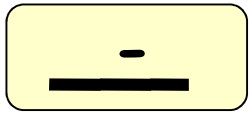
5. Activation
« Cancer-germline »



Many tumors



Germinal cells



Other normal cells

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Immunoprivileged

MAGE
BAGE
GAGE
RAGE
NY-ESO
MUCINS

Tumor Expression Profile of Cancer-Germline Genes

Genes	Metastatic melanoma	Lung carcinoma	Colorectal carcinoma	Breast carcinoma	Prostate carcinoma
MAGEA1	46	46	0	19	18
MAGEA3	74	47	17	13	18
MAGEA4	25	51	11	6	0
MAGEA12	62	30	11	13	5
MAGEC2	43	11	0	15	1 of 10‡
BAGE1	31	10	0	12	0
GAGE1	41	38	0	10	15
XAGE1B	43	2 of 3‡	4 of 12‡		
CTAG2	33	41	0	23	27
CTAG1	35	27	0	23	27
SSX2	50	0	26	19	25

BAGE1, B melanoma antigen 1; *CTAG*, cancer/testis antigen (*CTAG2* is also known as *LAGE1*; *CTAG1* is also known as *NYESO1*); *GAGE1*, G antigen 1; *MAGEA*, melanoma antigen family A; *SSX2*, synovial sarcoma X breakpoint 2; *XAGE1B*, X antigen family member 1B. *Percentage of tumours that express the gene.
‡The numbers of tested tumours are low, and the real numbers are shown.

Coulie. *Nat Rev Cancer* 2014; 14: 135

Potential of cancer-germline gene antigen vaccination

- Cancer germ-line gene antigens have not shown much therapeutic success so far.

- The response is most likely compromised by their highly heterogeneous expression in many tumors and low frequency in some cancers.

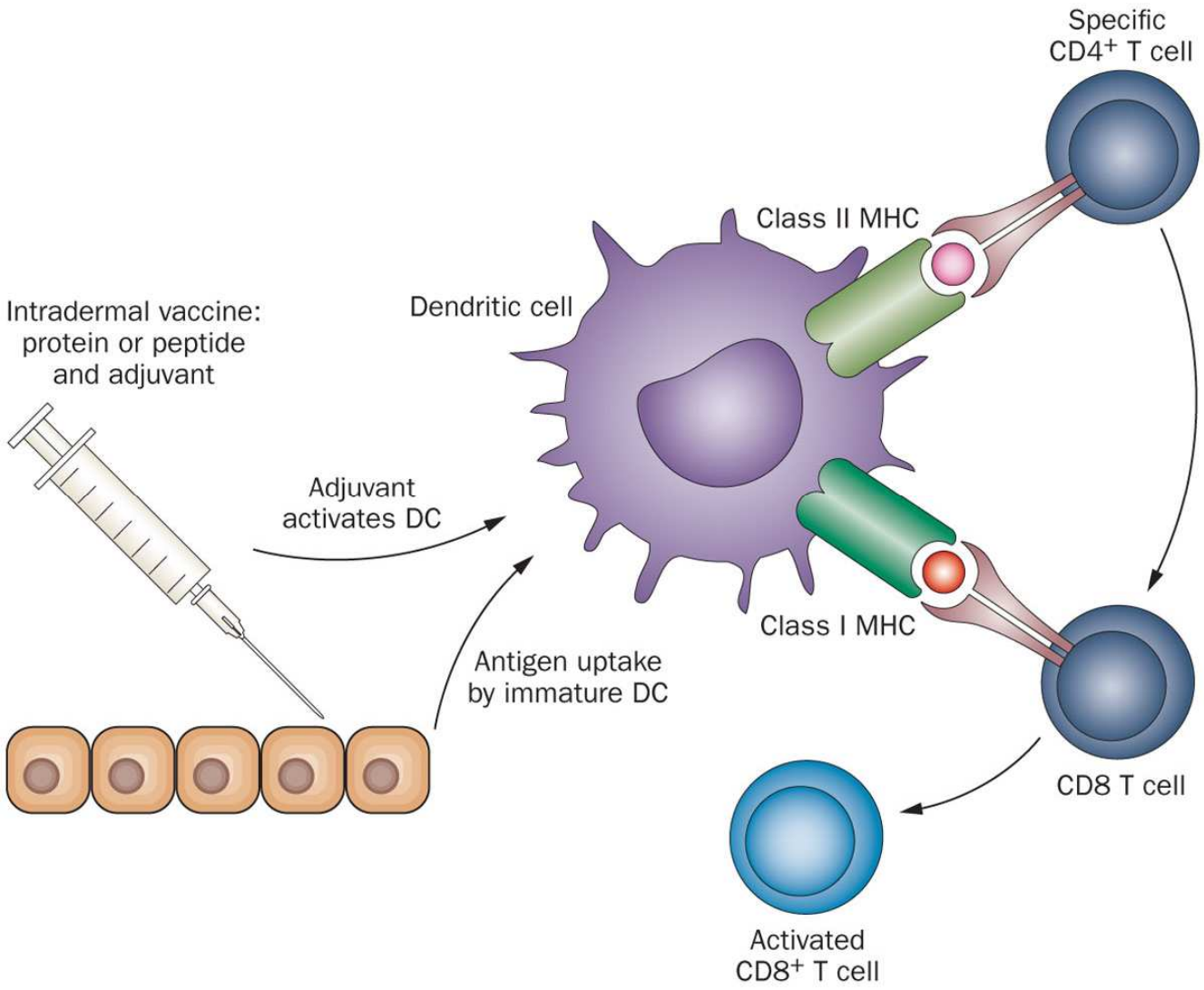
- Efforts are underway for tumor-cell-selective enhancement of cancer germ-line gene antigen expression using epigenetic modifiers.

Components of a Cancer Vaccine

- **Antigens** are targets of T cell immunotherapy
- **Adjuvants** are useful in directing cellular immune responses to these antigens
  - Antigen depot for prolonged release
  - Save antigen from degradation
  - Increase antigen uptake by APCs
  - Provide pro-inflammatory/pro-immunogenic milieu

Antigen	Adjuvant	Vector	Route
Whole tumor cells	Emulsifiers or surfactants: Oil (IFA), ASO_2, MF59, Montanide, QS21	Viral vectors	Injection
Irradiated tumor cell lysates	Particulates: ASO_4	Dendritic cells	Gene gun
Antigenic peptides	Mineral salts: Alum	Attenuated bacteria	Hydrodynamic delivery
Protein	Cytokines: GM-CSF, IL-12		Systemic infusion
	Innate agonists		Nasal spray
	Microbial products: BCG, CpG, lipid A		
	Antibodies		

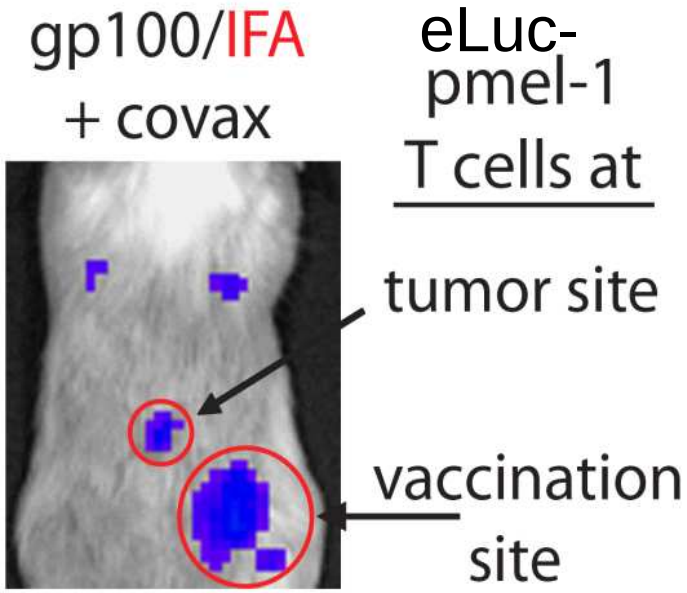
Cancer Vaccine: Mechanism of Action



Drake CG *et al. Nat Rev Clin Oncol,* 2013

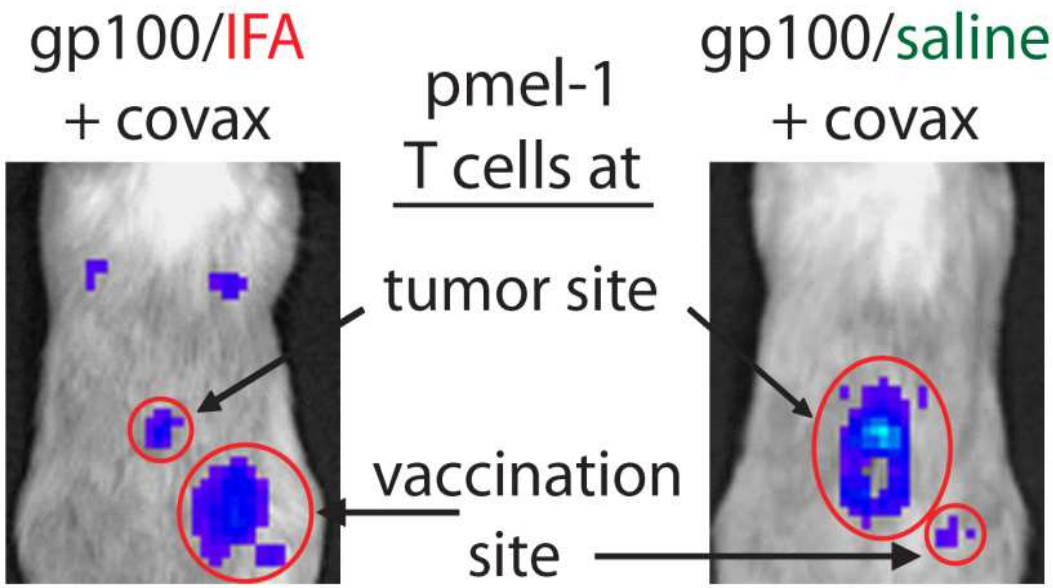
Advances in Cancer Vaccination approaches

Oil-based vaccines sequester T cells at the vaccination site



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

Water-based vaccines permit T cell accumulation in tumor



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

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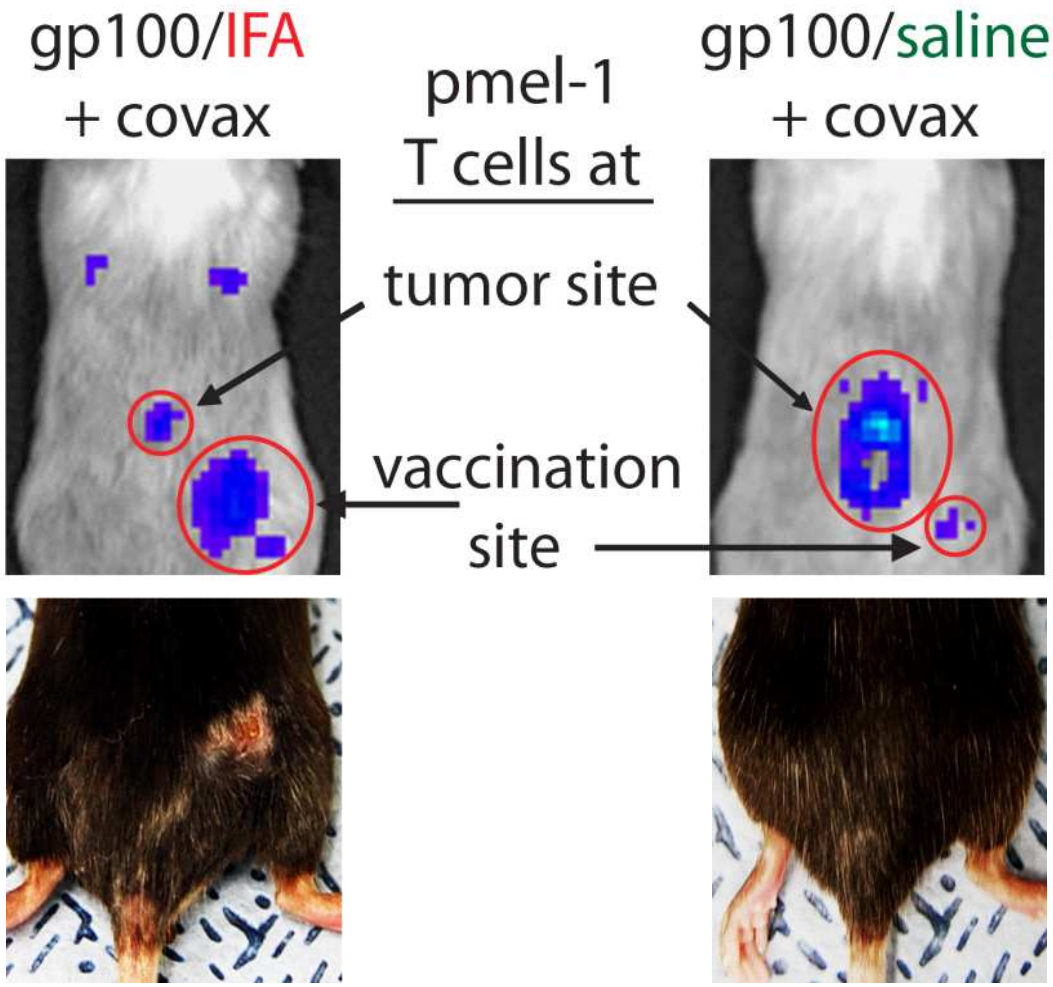
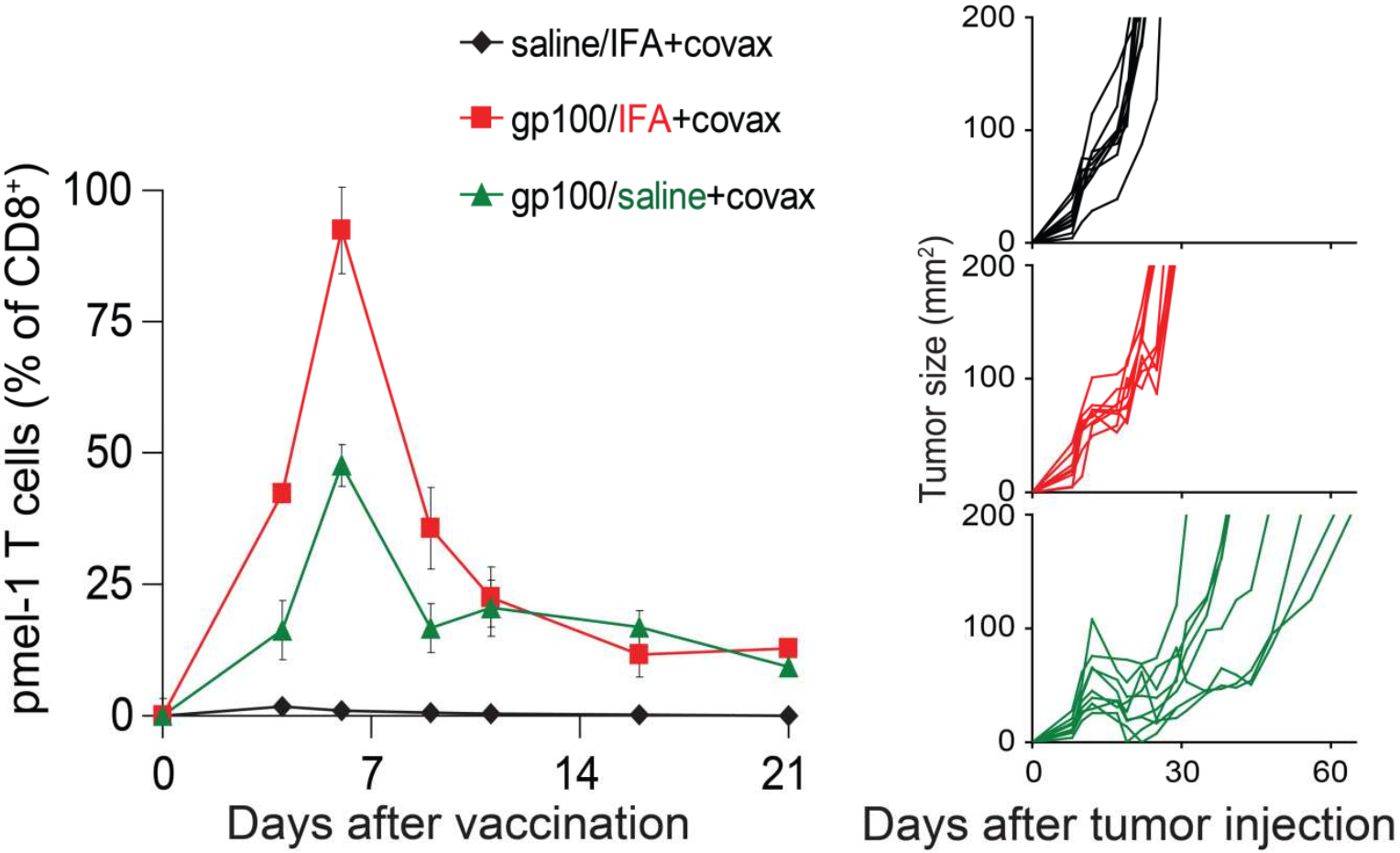


Hailemichael *et al*., Nat. Med. 13, 2013

Long-lived *versus* short-lived vaccine

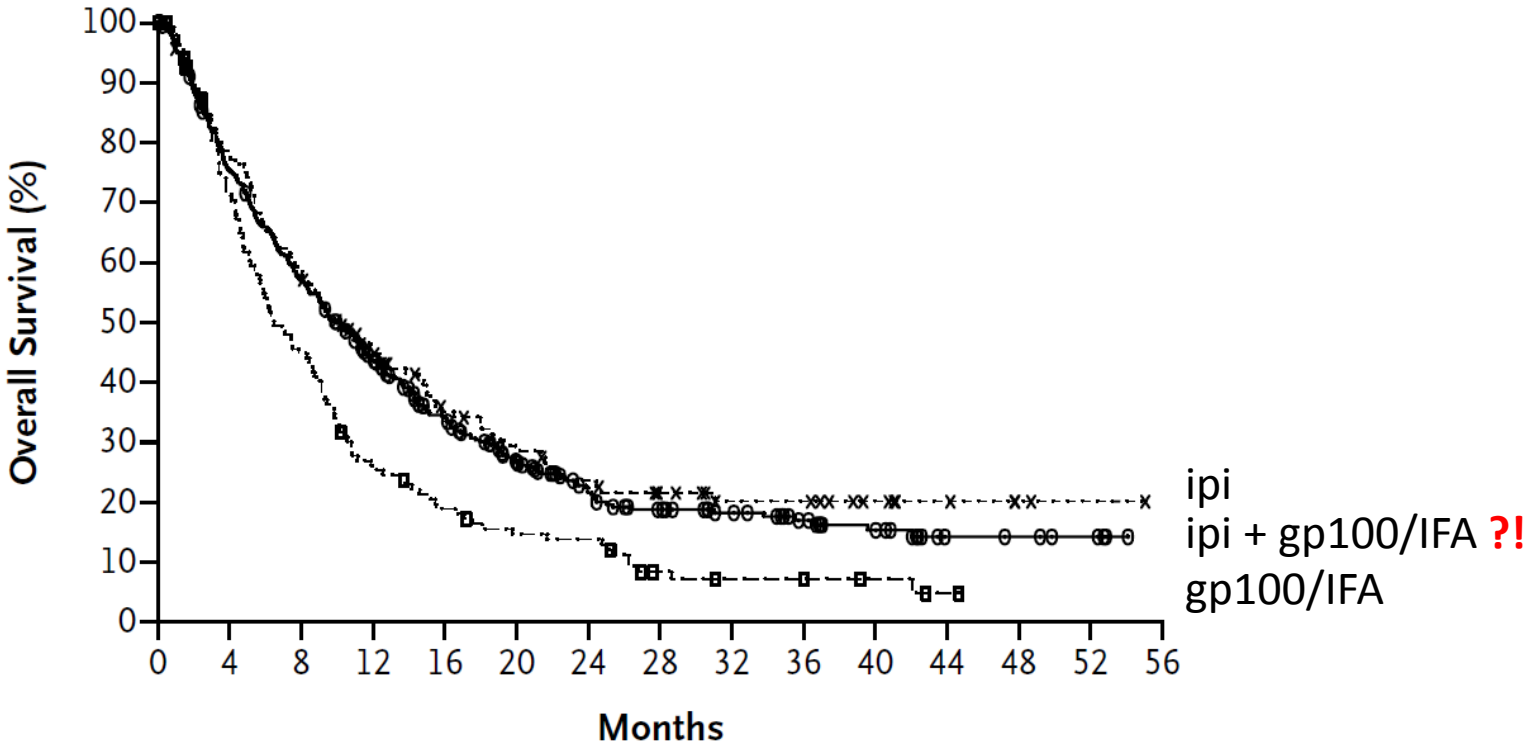


Hailemichael *et al*., Nat. Med. 13, 2013

Vaccines + Checkpoint Blockade

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

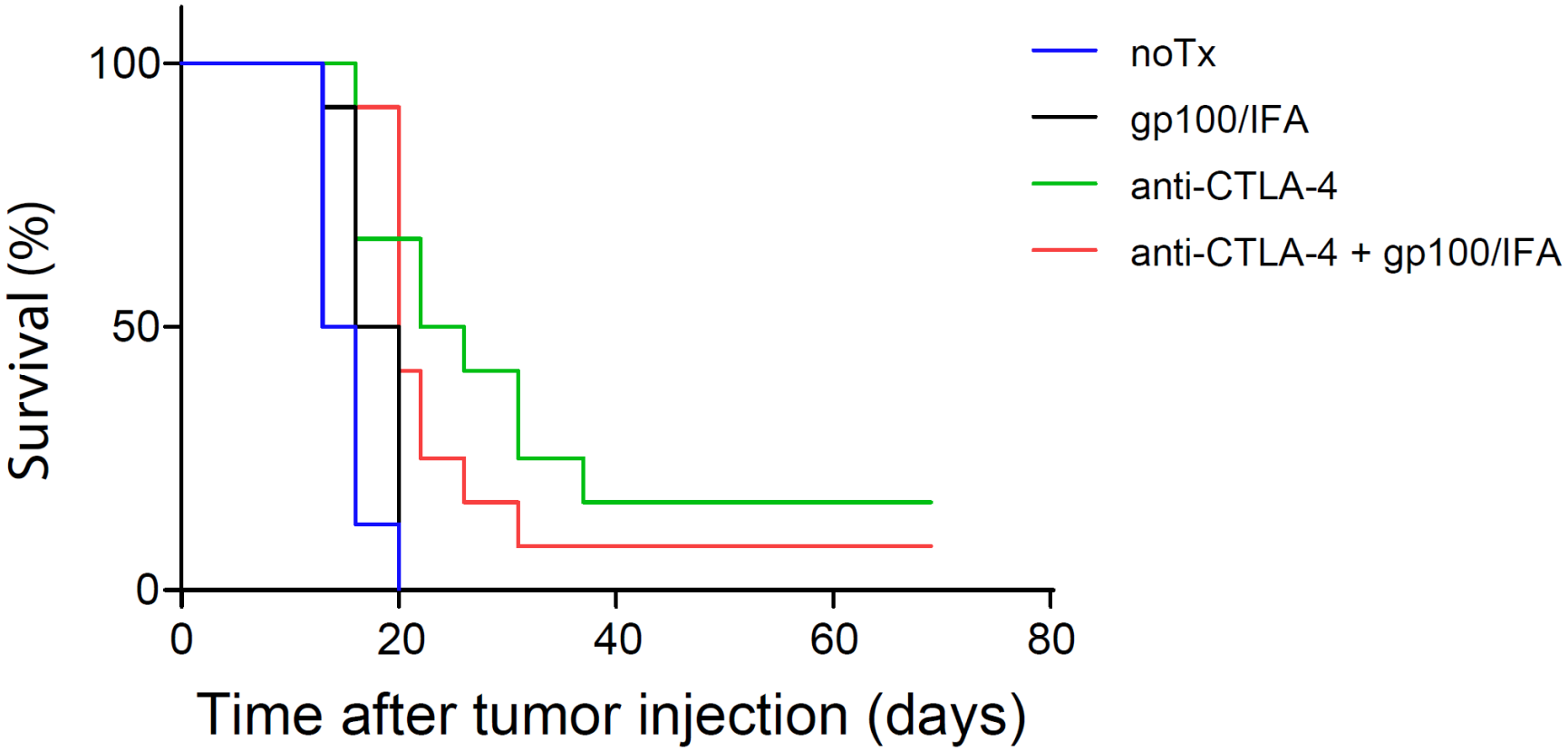
Improved survival with anti-CTLA-4 (ipilimumab) in patients with metastatic melanoma could not be extended with gp100 vaccination



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

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

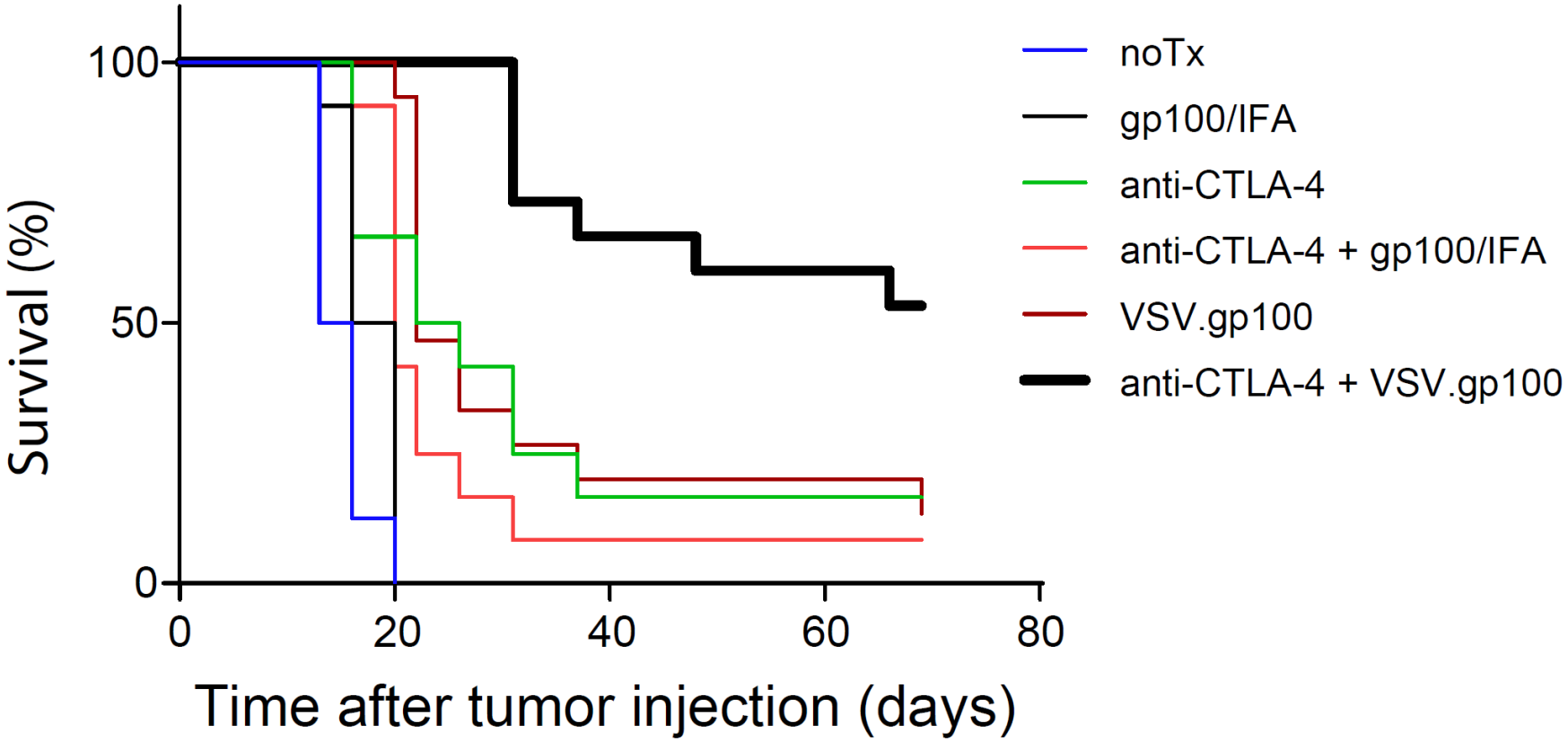
pmel-1 mouse model



Yared Hailemichael

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

pmel-1 mouse model



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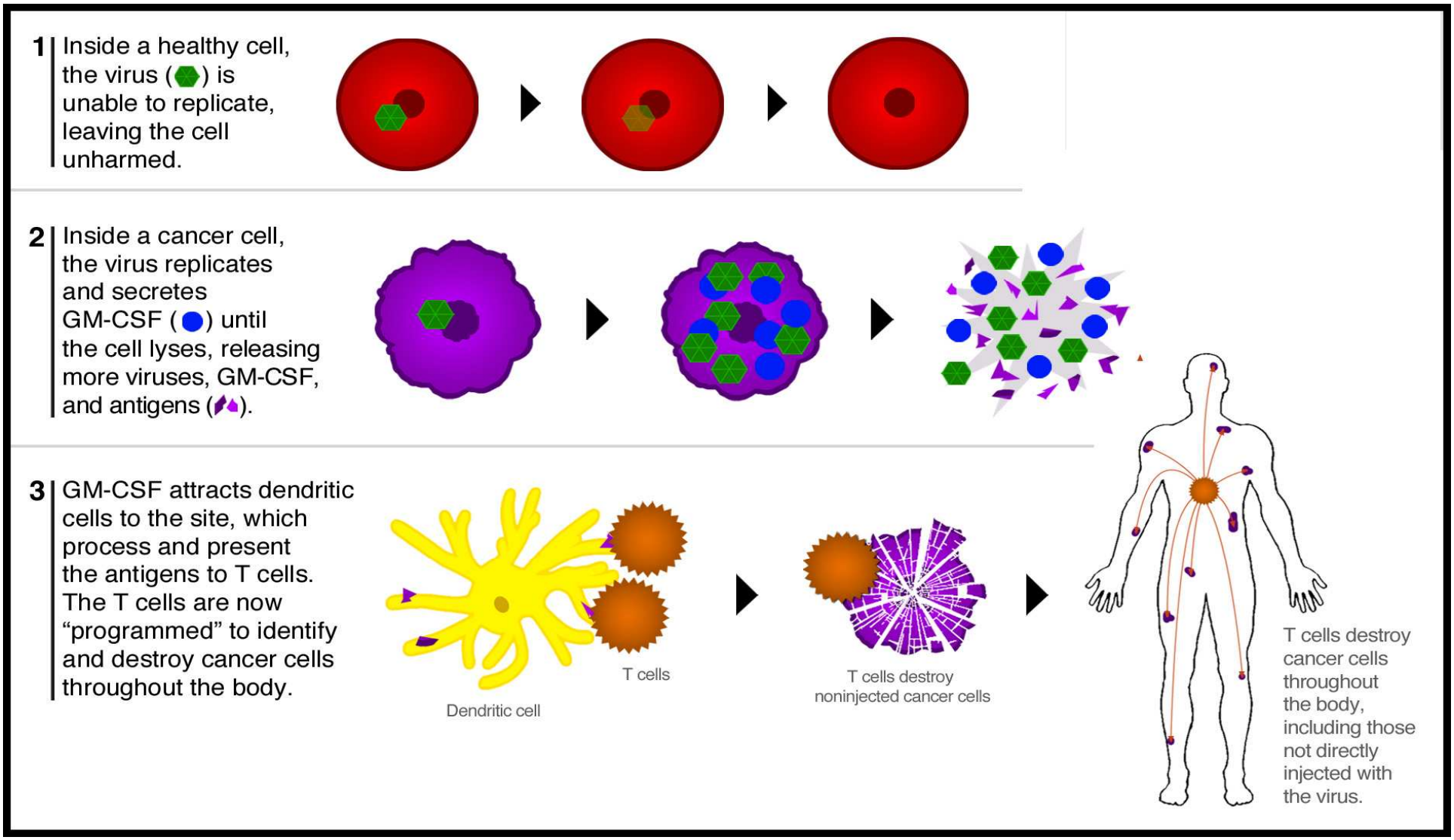
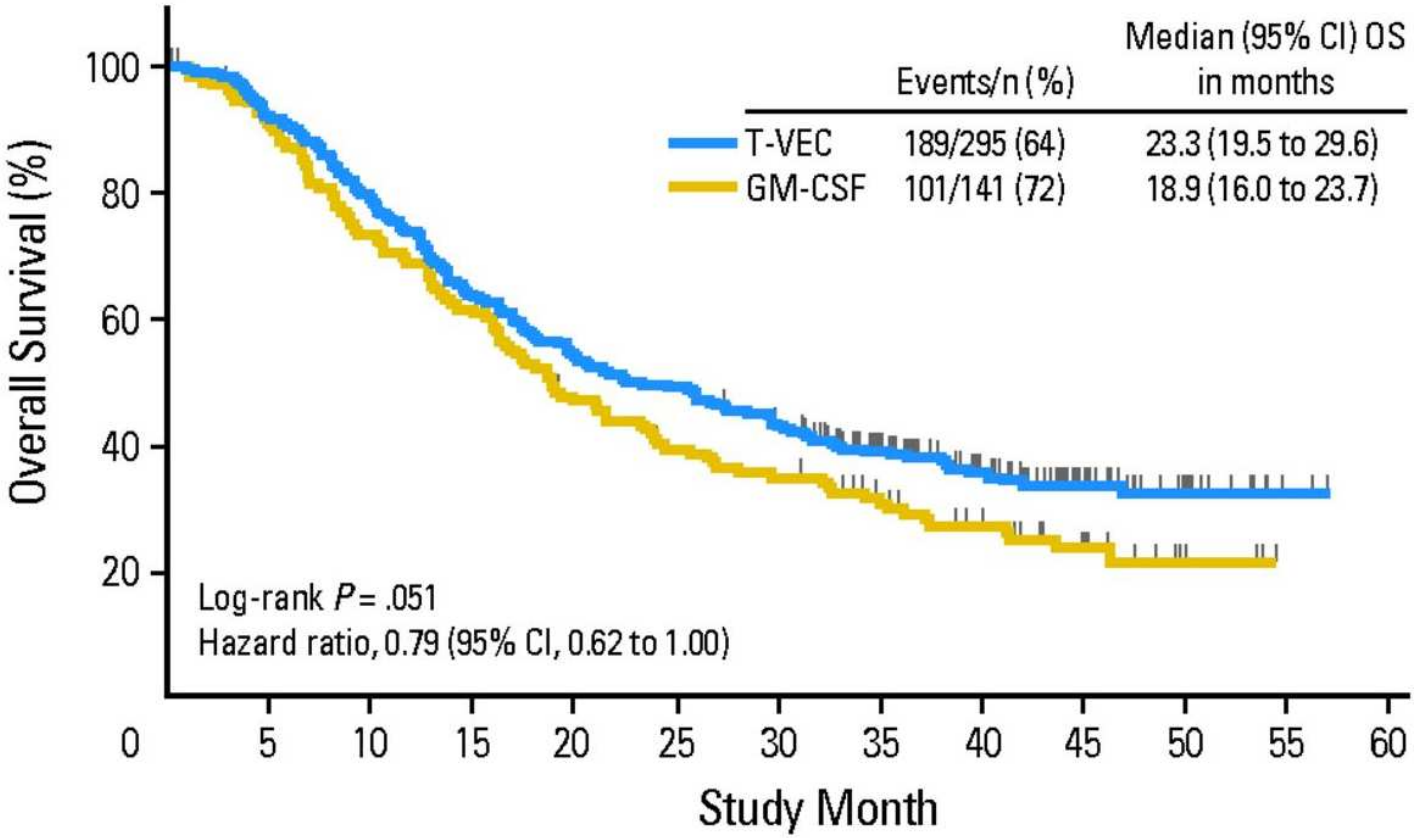
Oncolytic Virus Immunotherapy



T-Vec improves durable response rate in patients with advanced melanoma

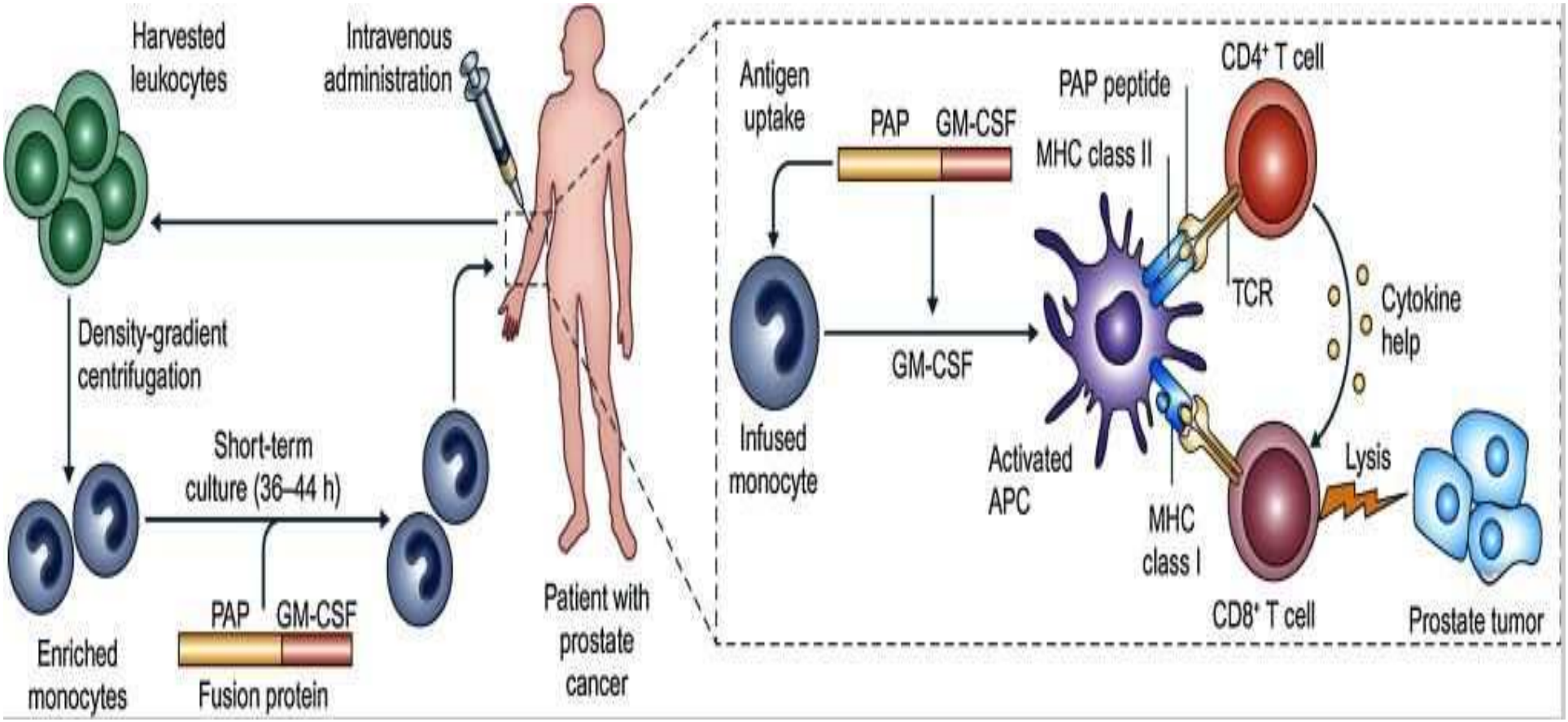
- T-Vec (Talimogene laherparepvec): a herpes simplex virus type 1—derived oncolytic immunotherapy
- Replicate within tumor cells and produce GM-CSF to support anti-tumor immune responses



Robert H.I. Andtbacka et al. *JCO* , May 26, 2015

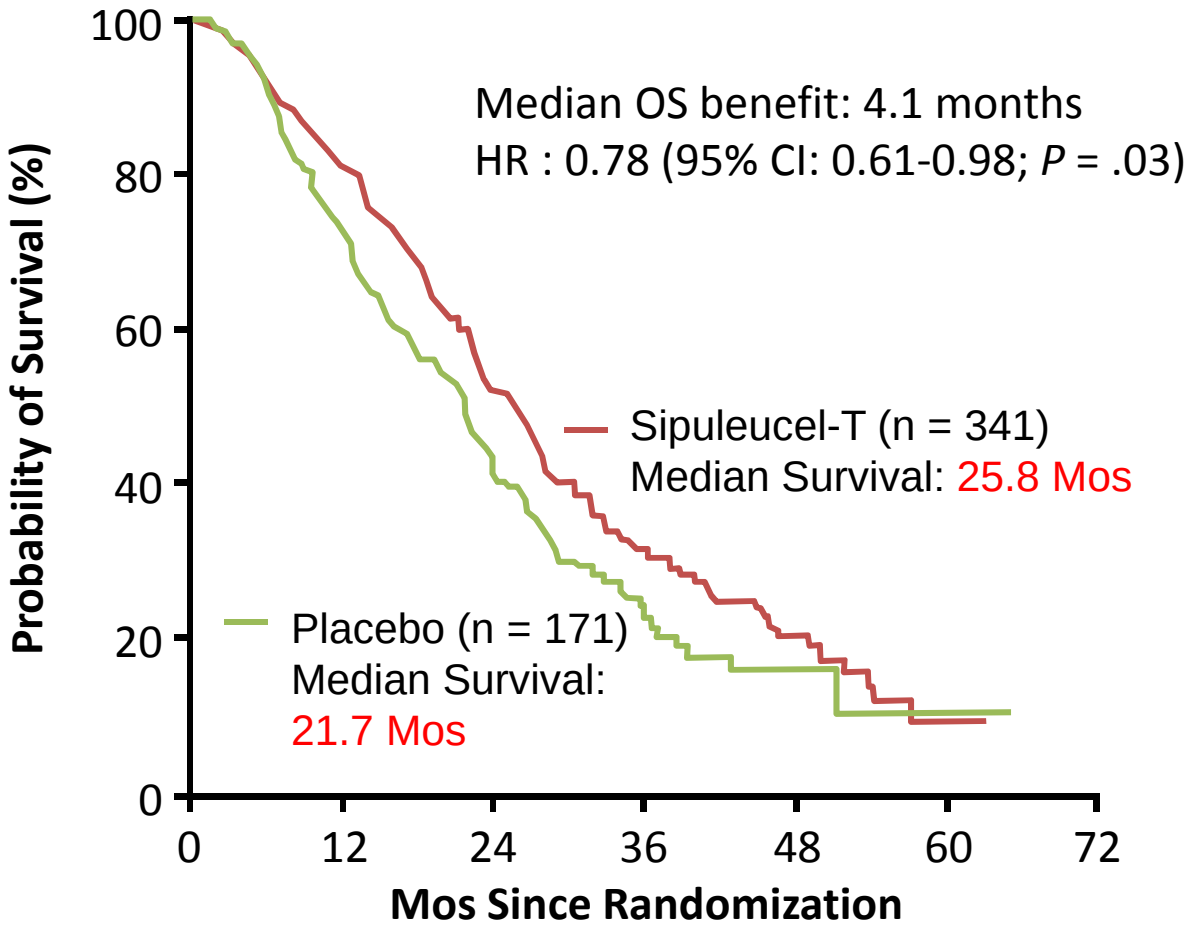
Sipuleucel-T Vaccination in mCRPC

<u>Sipuleucel-T</u>: Patient's leukapheresed cells exposed to recombinant fusion protein consisting of prostatic acid phosphatase (PAP) antigen and GM-CSF



Mulders PF et al. *Cancer Immunol Immunother.* 2015, 64: 655–663

Phase III IMPACT Study: Sipuleucel-T in mCRPC



Kantoff P et al. *New Engl J Med*. 2010,363:411-422

Therapeutic vaccines in clinical trials for lung cancer

Vaccine	Target /Composition	Status	Clinical Trial #
GV1001	**Targets the human telomerase reverse transcriptase, hTERT subunit of telomerase**	**A phase III study for patients with stage III NSCLC**	**NCT01579188**
Tergenpumatucel-L	**Consists of 3 human NSCLC cell lines genetically modified to express α-gal carbohydrates on cell surface to stimulate immune response**	**A phase II/III trial for NSCLC**	**NCT01774578**
TG4010	**Targets the MUC1 antigen**	**A phase II/III study for stage IV NSCLC.**	**NCT01383148**
DRibbles (DPV-001)	**Consists of over 25 tumour antigens including nine from the NCI's list of prioritized cancer antigens and multiple DAMPs, such as S100A8, nucleolin, calreticulin, HMGB1, HSP70, HSP90, DNAs and RNAs that bind to TLRs**	**A phase II trial for stage III NSCLC**	**NCT01909752**
MUC1	**Epithelial glycoprotein-based vaccine**	**A phase I/II trial for any stage of NSCLC**	**NCT01720836**
CV9202	**mRNA-derived NSCLC vaccine that expresses six tumour antigens**	**A phase I trial for stage IV NSCLC**	**NCT01915524**
Wilms tumour antigen (WT1)	**Recombinant WT1 peptides containing HLA-A2.1 binding anchor motifs that stimulate CTL responses**	**A phase II trial for mesothelioma after completing surgery and chemotherapy and/or radiation**	**NCT01265433**
TroVax	**Targets the tumour-associated antigen, 5T4, with a pox virus vector, widely expressed on solid cancers**	**A phase II trial for patients with mesothelioma**	**NCT01569919**

Shanker A, Dikov MM, Carbone DP. *Immuno-Oncology*. 2015,42:95-109

Lessons and Take Home Messages

- Cancer vaccines can have clinical impact.

To induce better clinical responses:

- Identify potent antigens:

  mutations/overexpressed/cancer-germline
- Formulation matters: possible T cell sequestration
- Add immunomodulators (cytokines, TLR agonists)
- Combination Vaccines: multiple immunostimulatory molecules
- Combine with checkpoint blockade antibodies