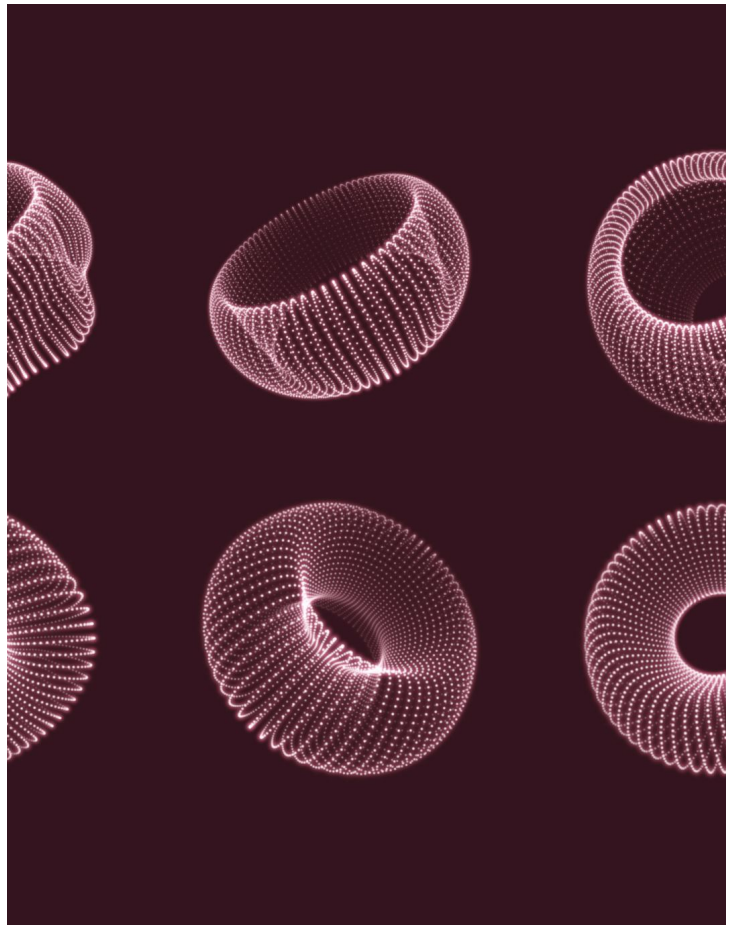


Vaccine Therapies for Cancer: A Challenging and Promising Landscape

ZHU Hengyan, PhD Year3 student

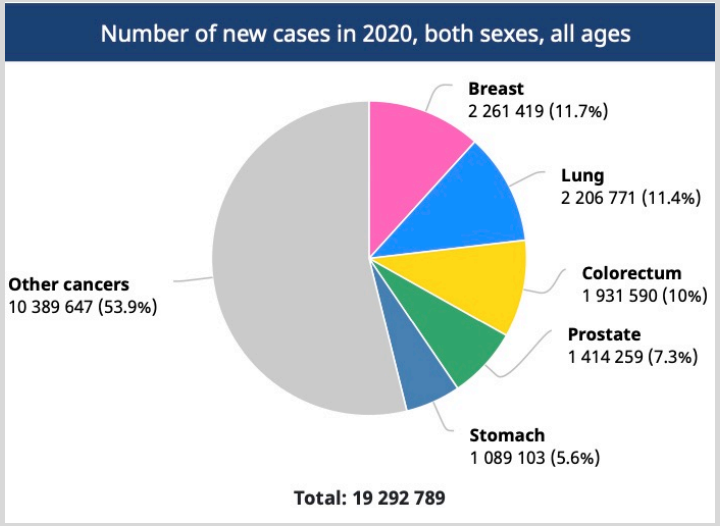
Supervisor: Prof. Zigui CHEN

6 Dec 2022

Outline

- Background and Introduction to cancer vaccines
- Working principles of cancer treatment vaccines
- Challenges of current cancer treatment vaccines
- Perspectives of future therapeutic cancer vaccines

Global cancer statistics and current treatments



- As GLOBOCAN 2020 report, new cancer cases diagnosed in 2020 were **19.3 million.**
- GLOBOCAN predicts that the number of cancer cases will increase to **28.4 million in 2040.** (SUNG, et al., CA: *a cancer journal for clinicians*, 2021)

- Current cancer treatments include surgery, chemo/radiotherapy, stem cell transplant, immunotherapy, et al.
- Cancer is still the 1st or 2nd leading cause of death in 112 of 183 countries with almost 10.0 million dying due to cancer in 2020.

(The Global Cancer Observatory, 2020)

Develop more efficient strategies for cancer treatments

Cancer vaccines: Prevent or Treat Cancer

1. Vaccines for preventing cancer: prevent healthy people from getting certain cancers caused by viruses.

HPV vaccine:

- Cervical, vaginal, and vulvar cancers
- Anal cancer

Hepatitis B vaccine: liver cancer

(https://www.openaccessgovernment.org/hpv-immunisation-programme-cervical-cancer/123681/)

2. Vaccines for treating cancers: treat existing cancer patients. (Treatment vaccines or therapeutic vaccines).

- Keep cancer from recurrence
- Destroy cancer cells after treatments end
- Stop a tumor from development or metastasis

Cancer immunotherapy

(https://onco.com/blog/cancer-vaccines-types-schedule-and-limitations/)

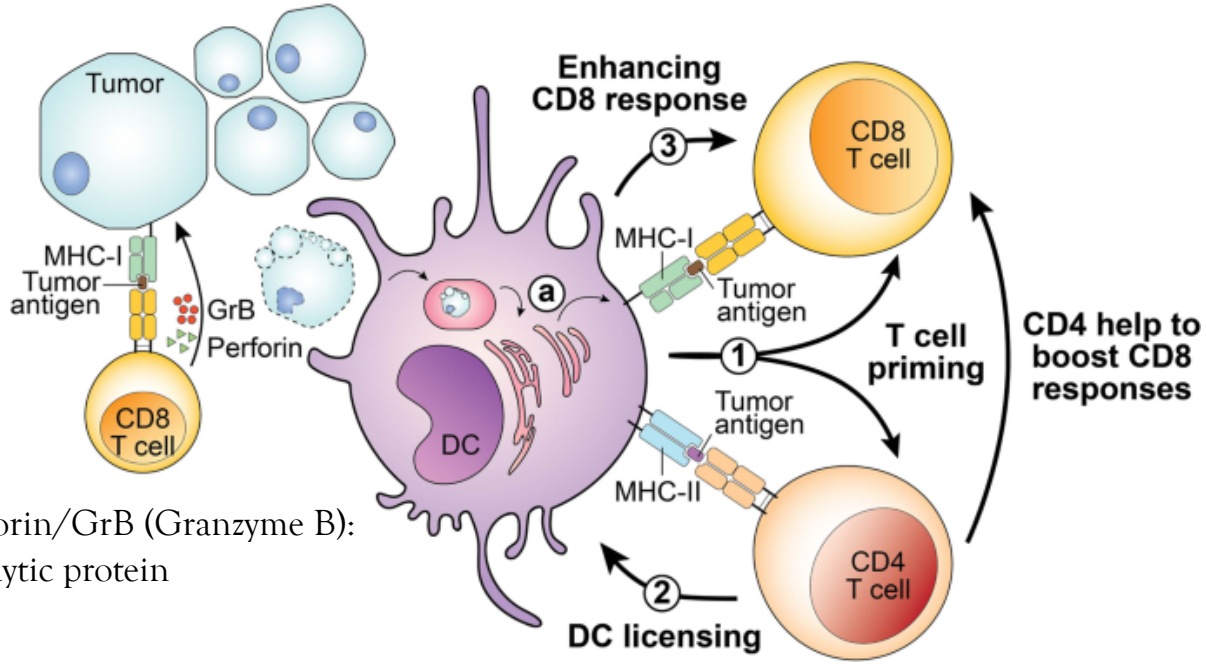
Antigen-presenting cells and anti-tumor immune response

- Dr. William Coley developed a rudimentary anti-cancer immune therapy consisting of heat-inactivated bacteria.

Dr. William Coley (1862-1936)

(Cann, Van Netthen, & Van Netthen, C., *Postgraduate medical journal*, 2003)

- Antigen-presenting cells (APCs) are a heterogeneous group of immune cells that mediate the cellular immune response by processing and presenting antigens for recognition by certain lymphocytes such as T cells.

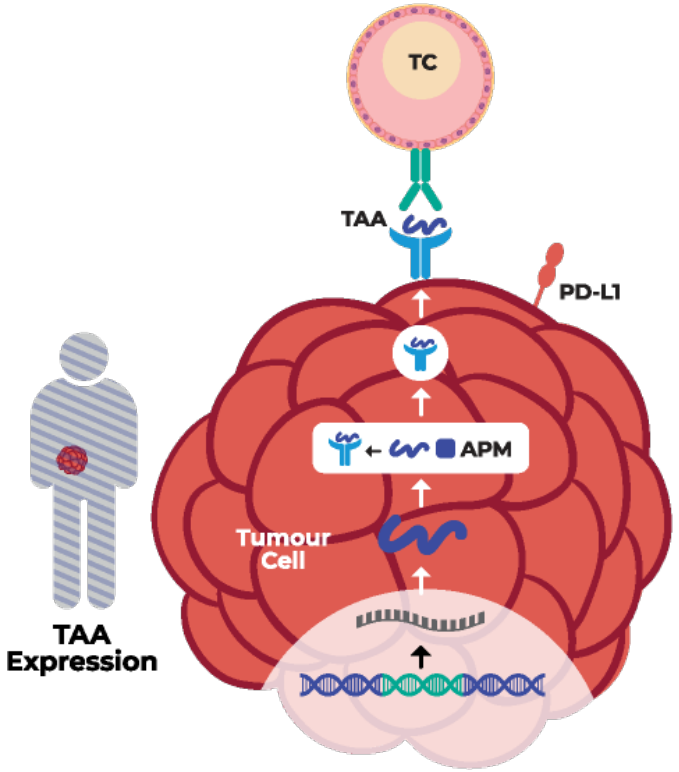


Perforin/GrB (Granzyme B): cytolytic protein

(Alfei, Ho, & Lo, *Oncogene*, 2021)

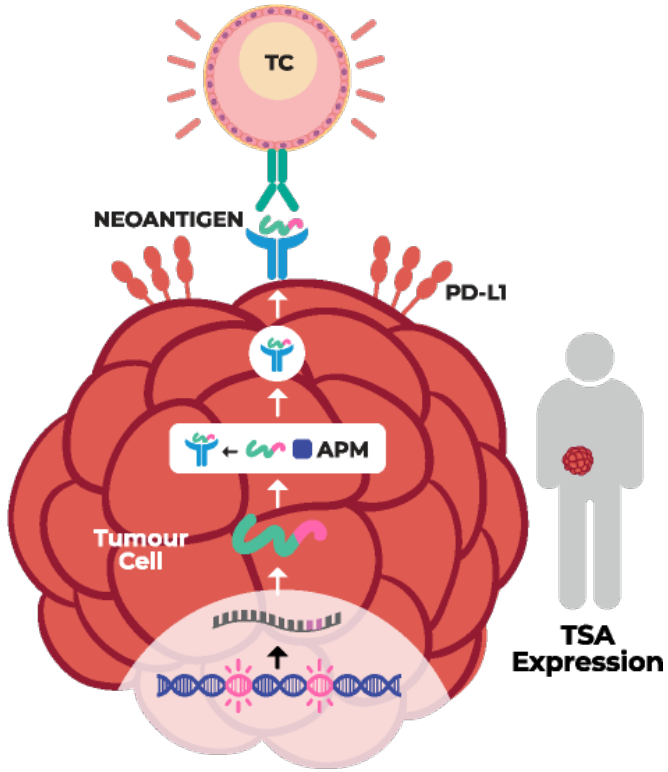
Cancer Therapeutic vaccine targets: TAAs and TSAs

- Aim to generate anti-tumor immune responses directed against tumor-associated antigens (TAAs) or tumor-specific antigens (TSAs).



TUMOR-ASSOCIATED ANTIGENS

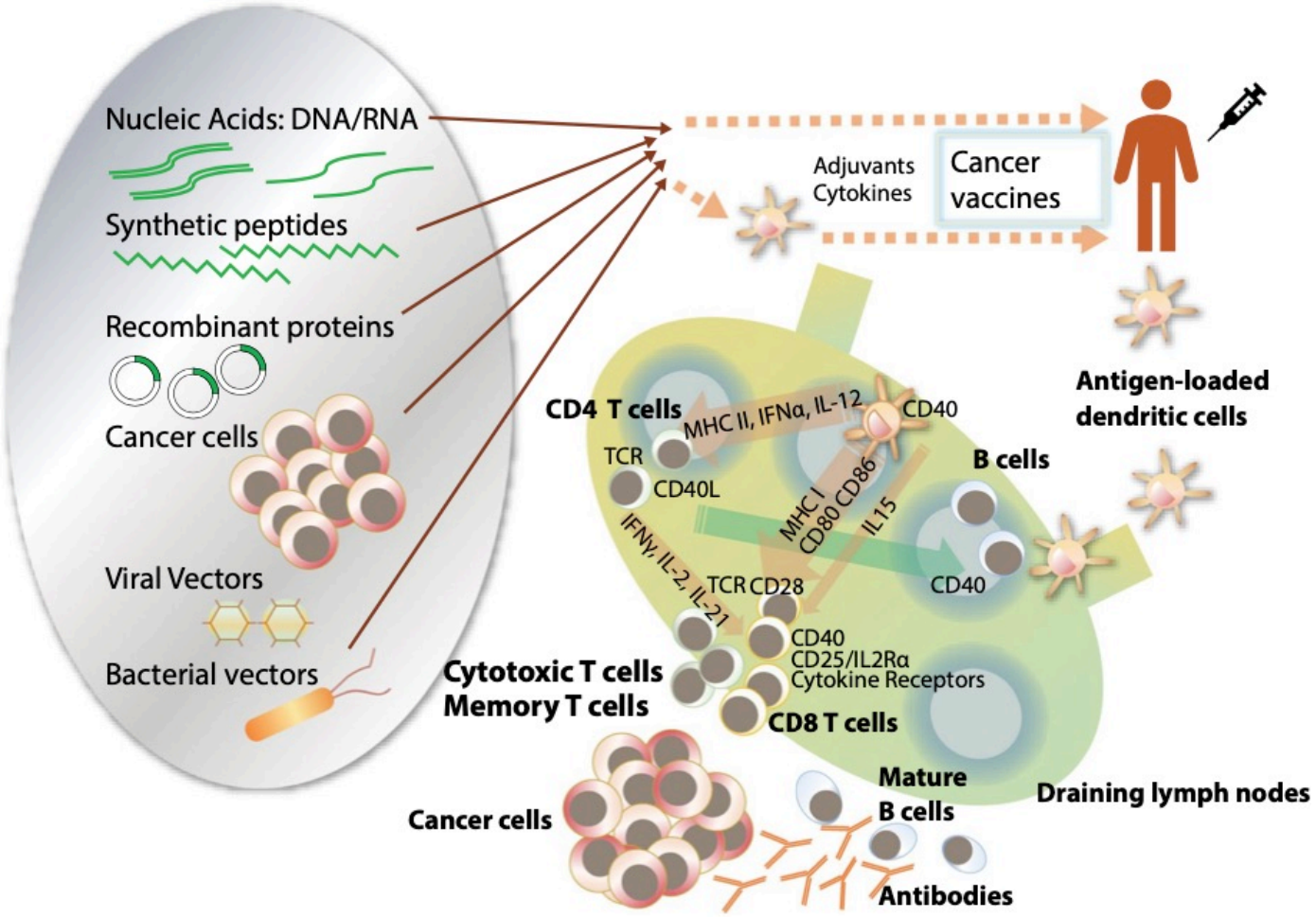
Tumor-Associated Antigens
Self-antigens expressed by tumor cells
Present in a subset of normal host cells
Arise mostly from genetic amplification or post-translational modifications
Tendency for expression that is higher and preferential for tumor cells
Example: Melanoma-associated antigen (MAGE) expressed in the testis along with malignant melanoma
Tumor-Specific Antigens
Expressed by tumor cells
Not present in normal host cells
Arise mostly from oncogenic driver mutations that generate novel peptide sequences (i.e. neoantigens)
Can also be generated by oncoviruses
Example: Alphafetoprotein (AFP) expression in germ cell tumors and hepatocellular carcinoma



TUMOR-SPECIFIC ANTIGENS

(https://www.auxitherapeutics.com/taa-t)

(Higgins, Bernstein, & Hodge, *Cancer biology & therapy*, 2009)



(Morse, Gwin, & Mitchell, *Targeted oncology*, 2021)

Different platforms of cancer vaccines

Peptide- and protein-based vaccines

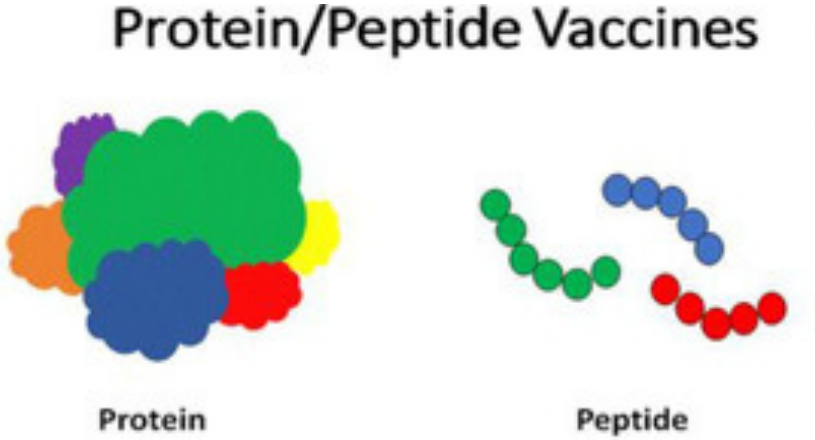
Cellular Vaccines

Genetic vaccine

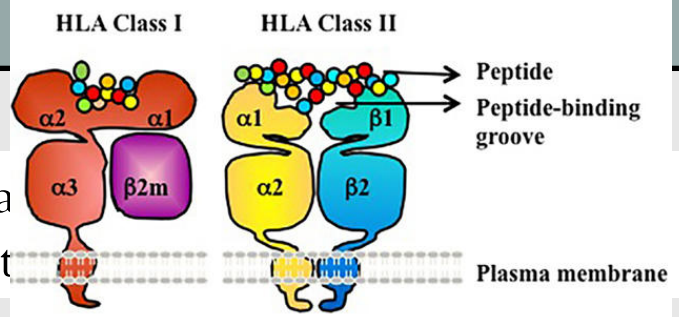
Other types of cancer vaccines

Peptide- and Protein-based vaccines

- The forms of delivered antigens are short amino acids (peptides) or larger protein bases.



Generate an immune response to TAAs that are uniquely or highly expressed on cancer cells

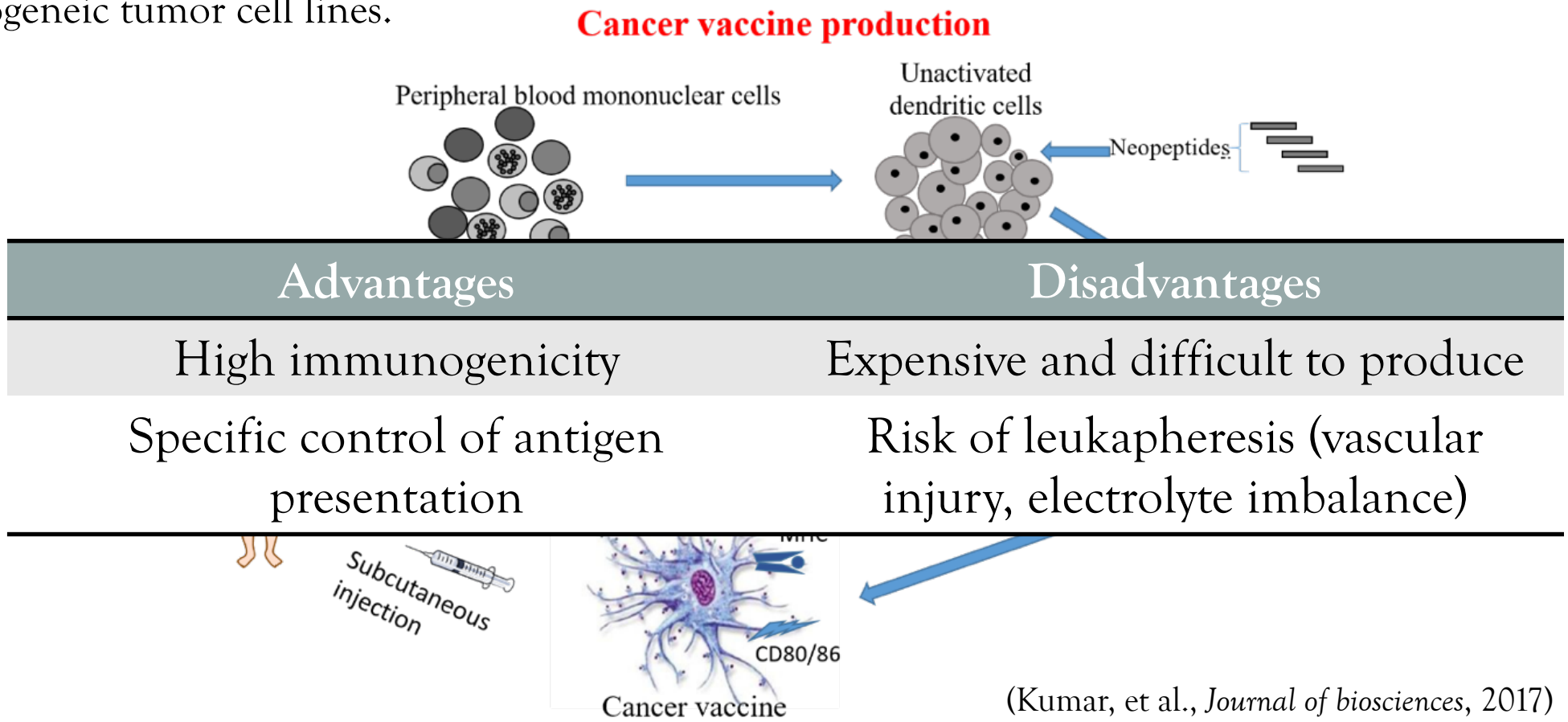


	Disadvantages
	Low/moderate immunogenicity
Widely a funct	Peptide: restricted to HLA subtype
Relati	Protein: hard identification for whole proteins

(DeMaria & Bilusic, *Hematology/Oncology Clinics* , 2019)

Cellular Vaccines

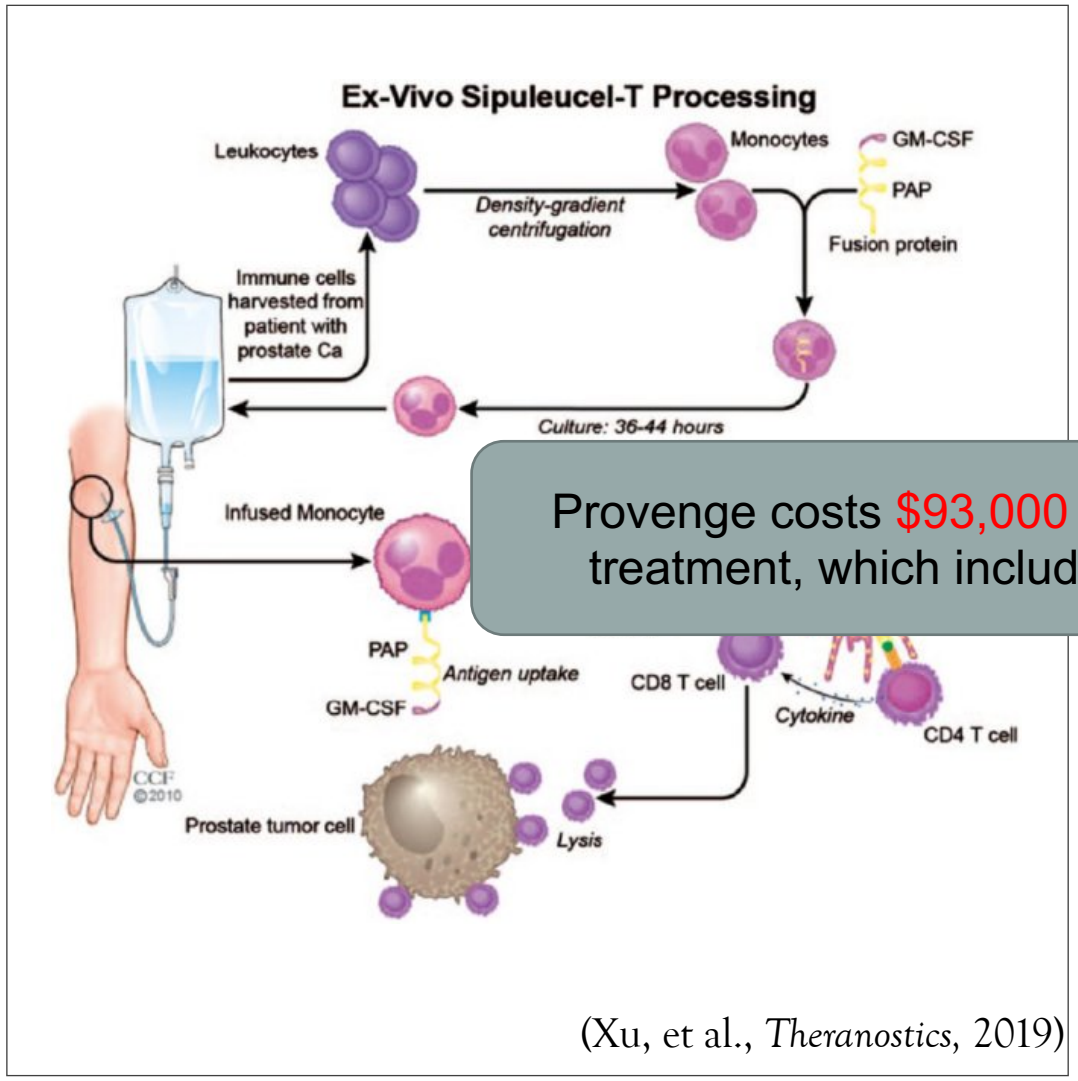
- Initial type of therapeutic cancer vaccine tested.
- Commonly include: Dendritic cells (DCs) loaded with tumor (neo)antigens, modified autologous cancer cells, and allogeneic tumor cell lines.



Advantages	Disadvantages
High immunogenicity	Expensive and difficult to produce
Specific control of antigen presentation	Risk of leukapheresis (vascular injury, electrolyte imbalance)

(Kumar, et al., *Journal of biosciences*, 2017)

1st therapeutic cancer vaccine: Sipuleucel-T (Provenge)



(Xu, et al., *Theranostics*, 2019)

Provenge costs $93,000 for the full six-week treatment, which includes three infusions

- Sipuleucel-T, sold under the brand name Provenge, is a cell-based cancer immunotherapy for **prostate cancer** (Cap).
- A course of treatment consists of **three basic steps:**

blood cells, primarily dendritic leukapheresis procedure.

s incubated with a fusion protein consisting of two parts:

The antigen prostatic acid phosphatase (**PAP**), which is present in 95% of prostate cancer cells and

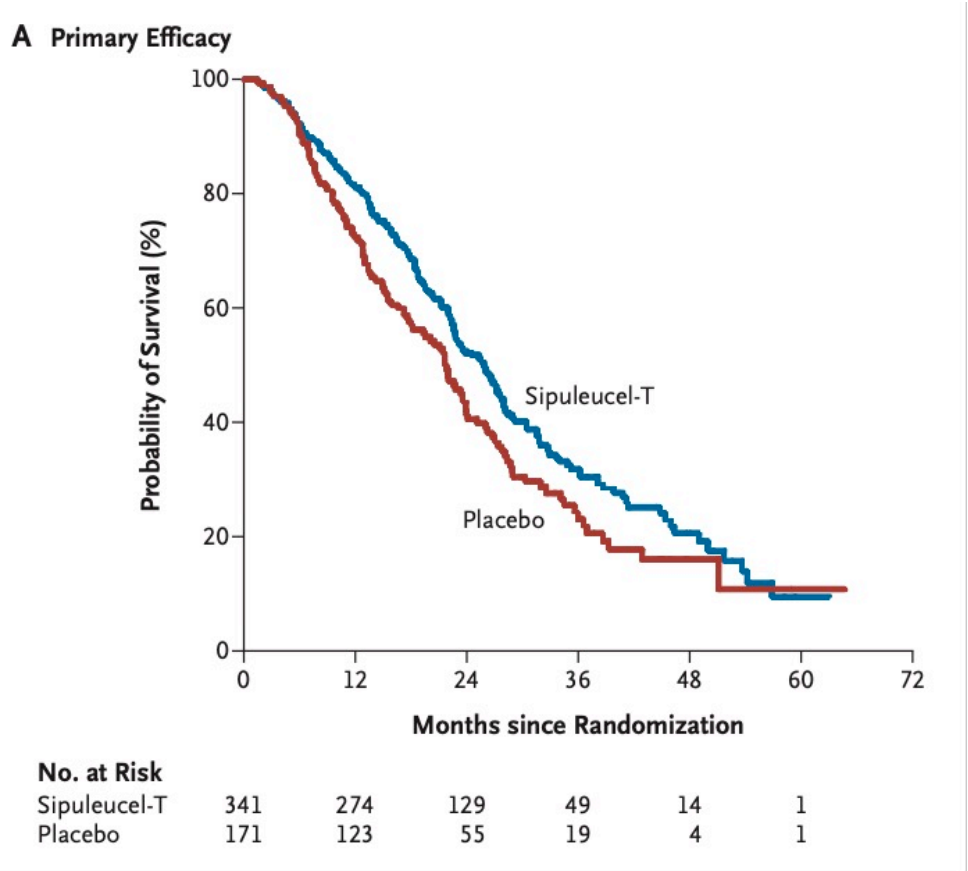
An immune signaling factor granulocyte-macrophage colony-stimulating factor (**GM-CSF**) helps the APCs to mature.

The activated blood product is reinfused into the patient.

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JULY 29, 2010 VOL. 363 NO. 5

Sipuleucel-T Immunotherapy for Castration-Resistant Prostate Cancer

Philip W. Kantoff, M.D., Celestia S. Higano, M.D., Neal D. Shore, M.D., E. Roy Berger, M.D., Eric J. Small, M.D., David F. Penson, M.D., Charles H. Redfern, M.D., Anna C. Ferrari, M.D., Robert Dreicer, M.D., Robert B. Sims, M.D., Yi Xu, Ph.D., Mark W. Frohlich, M.D., and Paul F. Schellhammer, M.D., for the IMPACT Study Investigators*



(Kantoff, et al., *New England Journal of Medicine*, 2010)

Phase III clinical trail of Sipuleucel-T

- Method: total 512 patients

341 sipuleucel-T vs. 171 placeboes administered intravenously every 2 weeks, for a total of three infusions.

- Primary endpoints: overall survival, analyzed by means of levels of serum prostate-specific antigen (PSA) and lactate dehydrogenase.
- Results:

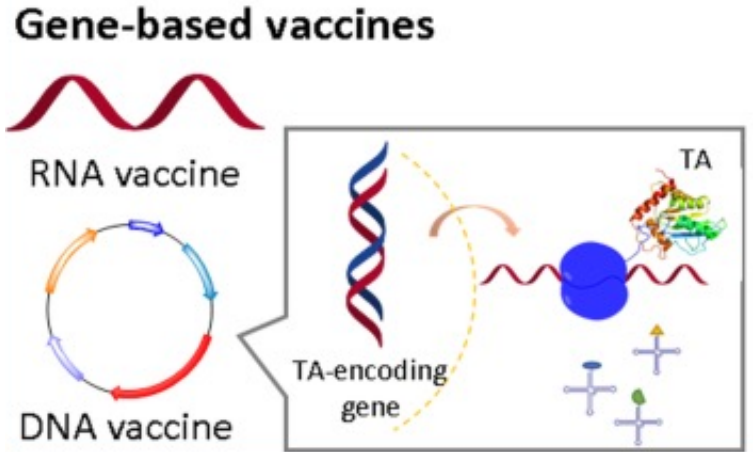
⇩22% in the risk of death (P=0.03).

⇧4.1-month improvements in median survival

⇧3-years survival probability (31.75% vs. 23.0%)

Genetic Vaccines

- DNA/RNA-based cancer vaccines: genes which are capable of tumor antigen coding.

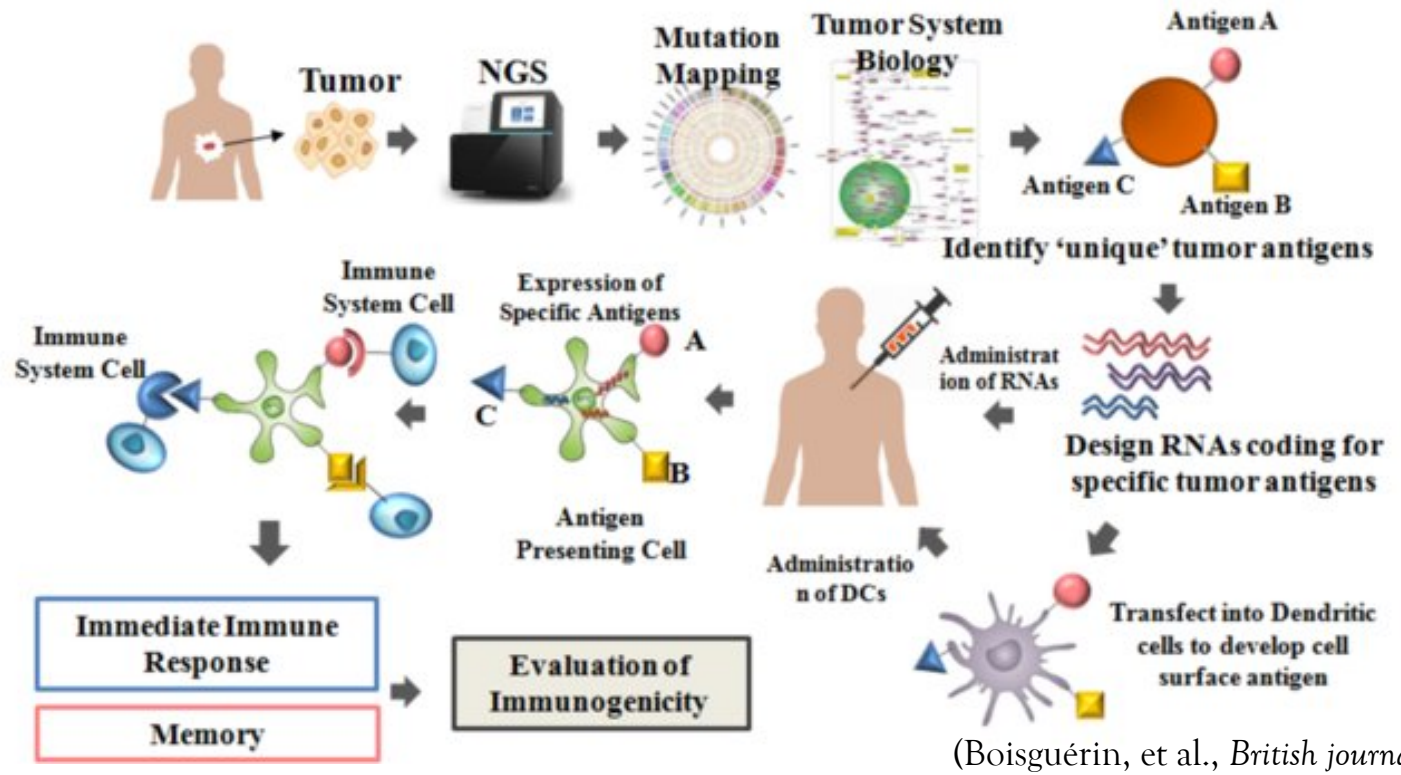


Advantages	Disadvantages
Easy designs of specific and multiple antigens	DNA and RNA: could be immunostimulatory by themselves (hard to keep stable)
Not restricted to HLA-patient type	Requires specific transportation/storage conditions

(Aurisicchio & Ciliberto, *Expert opinion on biological therapy*, 2012)

Development of personalized RNA-based cancer vaccines

- RNAs encoding for unique tumor antigens could be either **injected into the human body** or **transfected into DCs to develop cell surface antigens**.
- Presentation of antigens by APCs will promote the interactions between APCs and immune system cells, through the interactions of antigens and T cell receptors.



(Boisguérin, et al., *British journal of cancer*, 2014)

mRNA vaccine for cancer immunotherapy

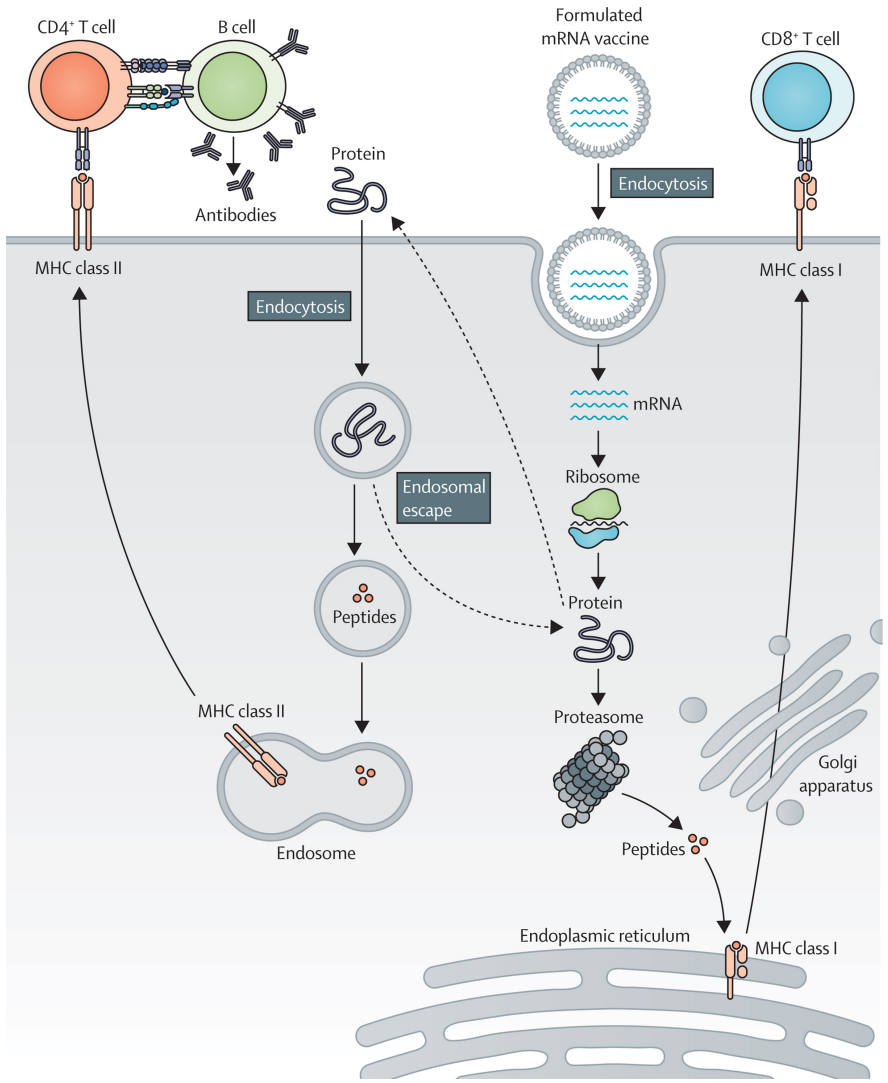
- mRNA cancer vaccine: high potency, safe administration, rapid development potentials, and cost-effective manufacturing.
- During vaccination, **naked or vehicle-loaded mRNA** vaccines efficiently express tumor antigens in antigen-presenting cells (APCs), facilitate APC activation and innate/adaptive immune stimulation.

- The advantages of mRNA over DNA as a cancer vaccine:

1. mRNAs can be translated in both dividing and non-dividing cells,. **The rate and magnitude of protein expression of mRNA** are typically higher than DNA vaccines

2. Unlike DNA vaccines, mRNA vaccines cannot integrate into the genome sequence, **thus free of insertional mutagenesis**.

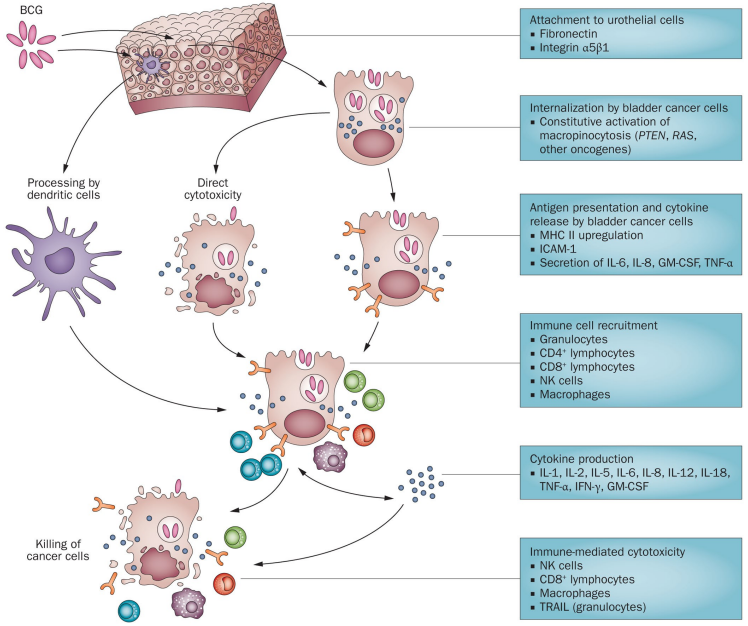
(Lorebrzeb, et al., *The Lancet Oncology*, 2022)



Other types of vaccines (Viral/Bacterial-based vaccine)

- Do not deliver defined tumor antigens to generate anti-tumor immunity
- Two approved cases:

Mycobacterium bovis bacillus Calmette–Guérin (BCG) is approved for the treatment of early-stage of the bladder cancer.



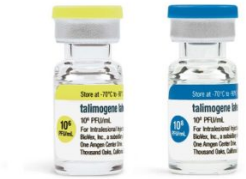
(Redelman-Sodo, Glickman, & Bochner, *Nature Reviews Urology*, 2014)

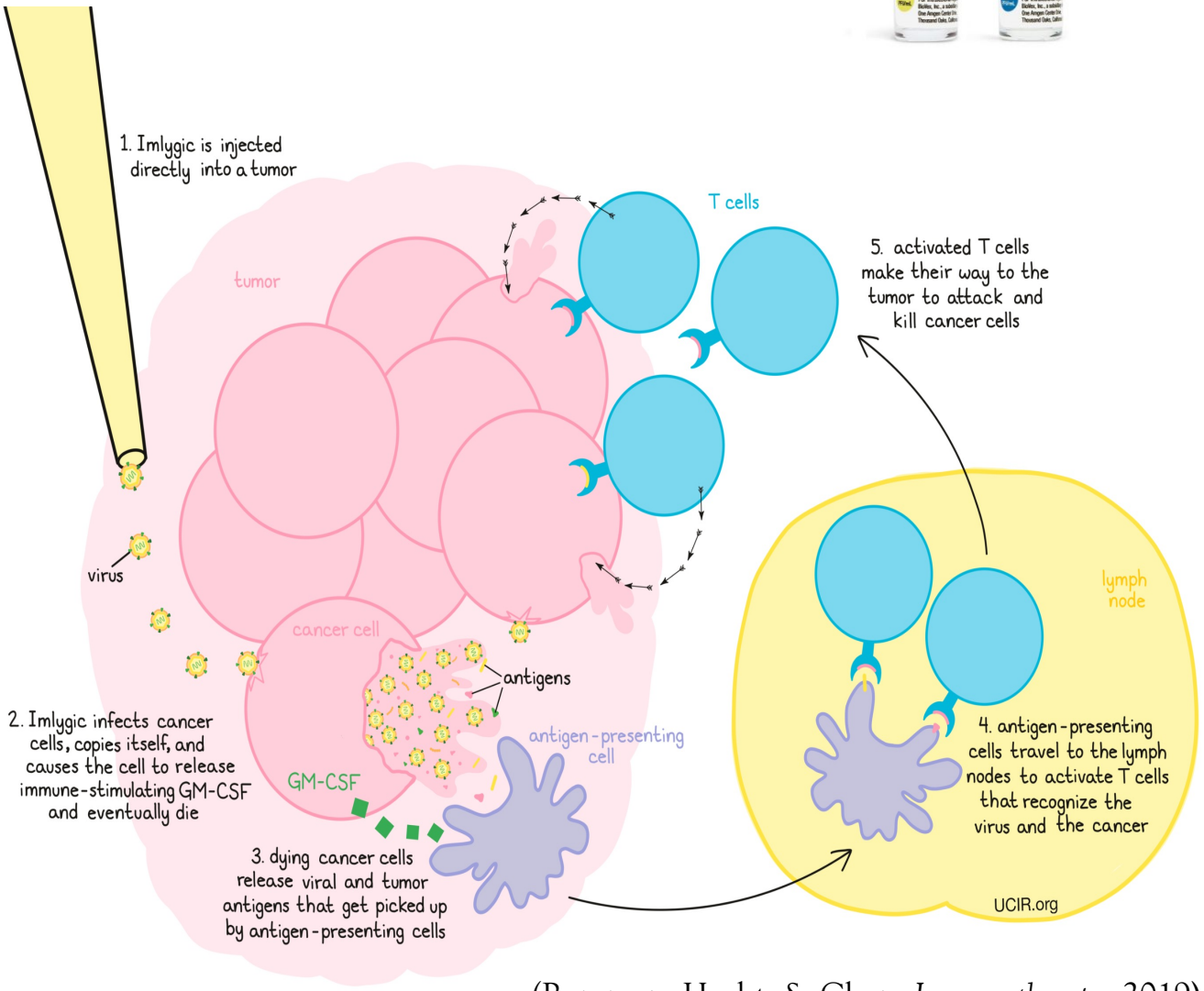
Total median costs at 1 year from the start of BCG induction therapy were $29,459; 2 years, $55,267; and 5 years, $117,361.

(Williams, et al., *JAMA network open*, 2021)

The oncolytic viral vaccine T-VEC, a herpes virus genetically modified to express **GM-CSF**, was licensed for the treatment of patients with unresectable melanoma.

Imlygic
(Talimogene laherparepvec)





(Ramman, Hecht, & Chan, *Immunotherapy*, 2019)

Viral-based cancer vaccine: Talimogene laherparepvec (T-vec)

- Talimogene laherparepvec, sold under the brand name **Imlygic**, is a herpes virus genetically modified to express **GM-CSF** used to treat melanoma.
- It is injected directly into a subset of lesions which generates a systemic immune response against the recipient's cancer.
- The makers of T-VEC have estimated the treatment will cost on average **$65,000.**

Response	T-VEC (n = 295)	GM-CSF (n = 141)	P
DRR			< .001
Patients with durable response, No.	48	3	
DRR, %*	16.3	2.1	
95% CI	12.1 to 20.5	0 to 4.5	
Unadjusted odds ratio	8.9		
95% CI	2.7 to 29.2		
ORR			< .001†
CR			
No.	32	1	
%	10.8	< 1	
PR			
No.	46	7	
%	15.6	5.0	
ORR, %*	26.4	5.7	
95% CI	21.4 to 31.5	1.9 to 9.5	

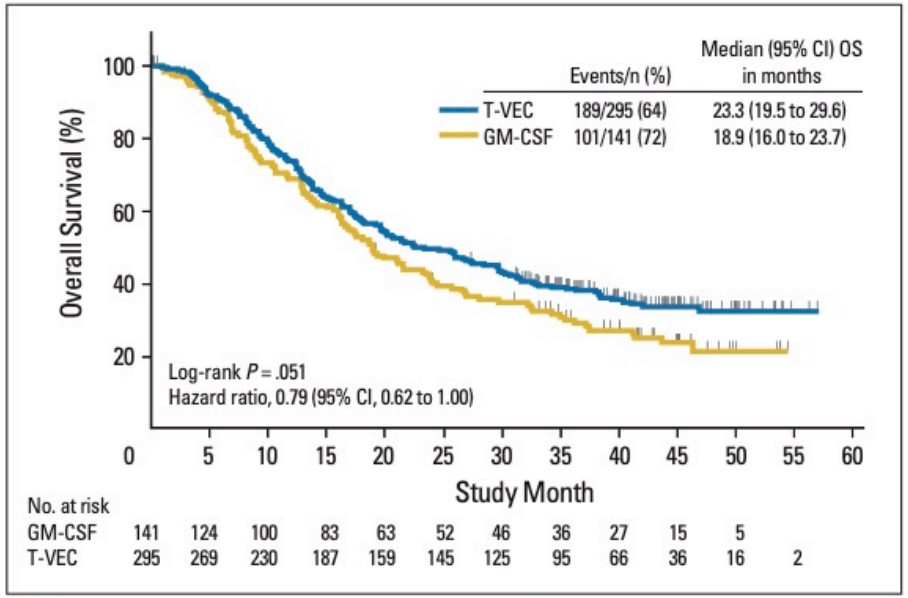
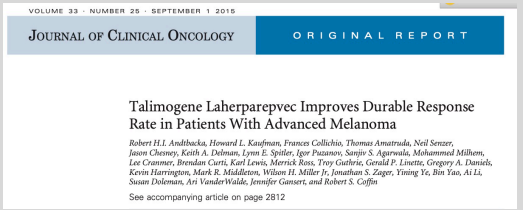


Fig 3. Primary analysis of overall survival (OS) in intent-to-treat population. GM-CSF, granulocyte macrophage colony-stimulating factor; T-VEC, talimogene laherparepvec.

(Andtbacka, et al., *Journal of clinical oncology*, 2015)

Phase III clinical trail of Talimogene Laherparepvec


VOLUME 33 · NUMBER 25 · SEPTEMBER 1 2015

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Talimogene Laherparepvec Improves Durable Response Rate in Patients With Advanced Melanoma

Robert H.I. Andtbacka, Howard L. Kaufman, Frances Collichio, Thomas Amatruda, Neil Senzer, Jason Chesney, Keith A. Delman, Lynn E. Spitler, Igor Puzanov, Sanjiv S. Agarwala, Mohammed Milhem, Lee Cranmer, Brendan Curti, Karl Lewis, Merrick Ross, Troy Guthrie, Gerald P. Linette, Gregory A. Daniels, Kevin Harrington, Mark R. Middleton, Wilson H. Miller Jr, Jonathan S. Zager, Yining Ye, Bin Yao, Ai Li, Susan Doleman, Ari VanderWalde, Jennifer Gansert, and Robert S. Coffin

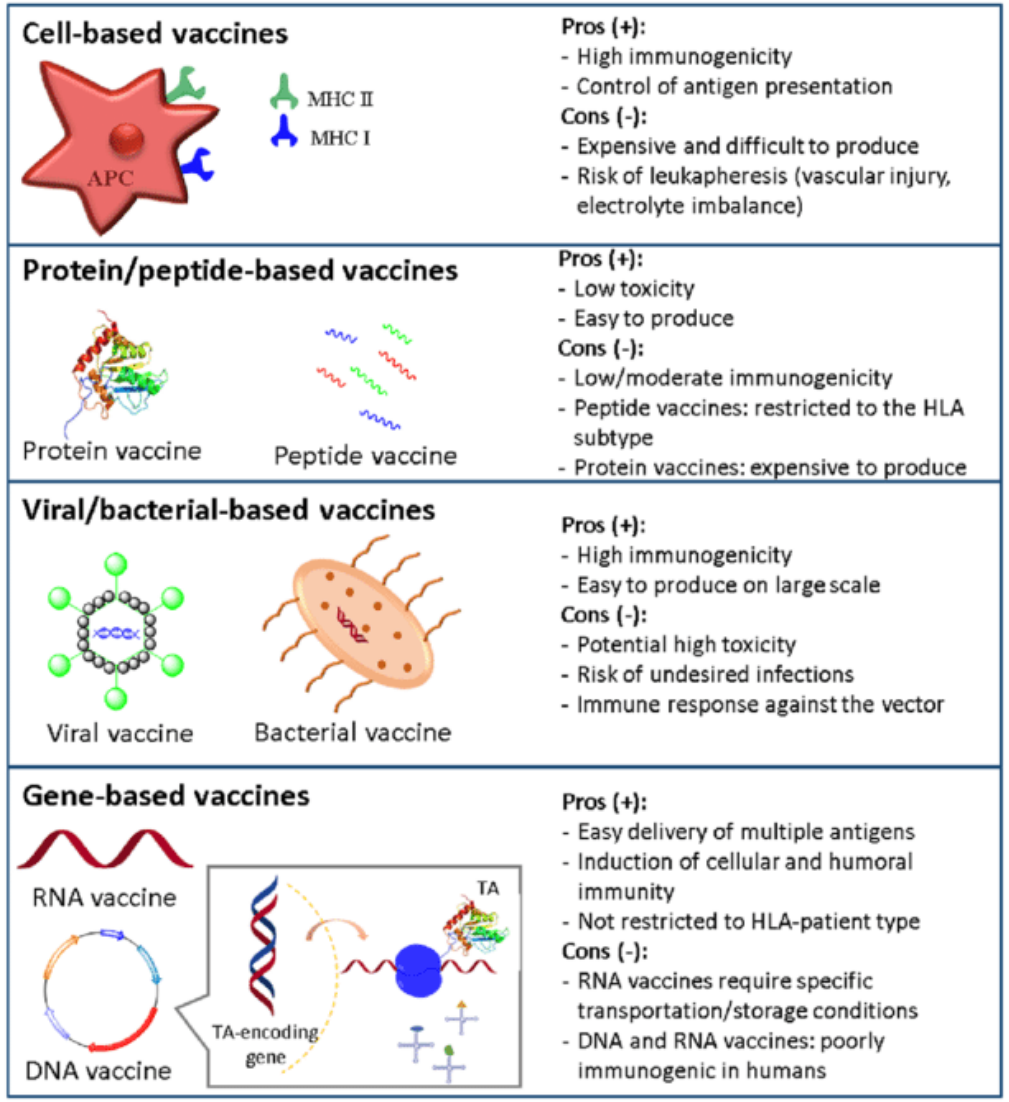
See accompanying article on page 2812

- Method: 436 Patients with injectable melanoma that was not surgically resectable were randomly assigned at a two-to-one ratio to intralesional T-VEC or subcutaneous GM-CSF.
- The primary end point was **durable response rate (DRR**; objective response lasting continuously 6 months) per independent assessment. Key secondary endpoints included **overall survival (OS) and overall response rate**.

⇧ DRR: 16.3% T-VEC vs. 2.1% GM-CSF

⇧ Median OS: 23.3 months T-VEC vs. 18.9 months GM-CSF

Differences among 4 cancer vaccine platforms



(Lopes, Vandermeulen, & Préat, *Journal of Experimental & Clinical Cancer Research*, 2019)

Challenges for cancer treatment vaccines

- A lack of response to the therapy (Primary) or following initial responsiveness of tumors to treatments (Secondary).
- Tumor intrinsic mechanisms: determined by the trials of the tumor cell itself
- Tumor extrinsic mechanisms: involve the tumor stromal components

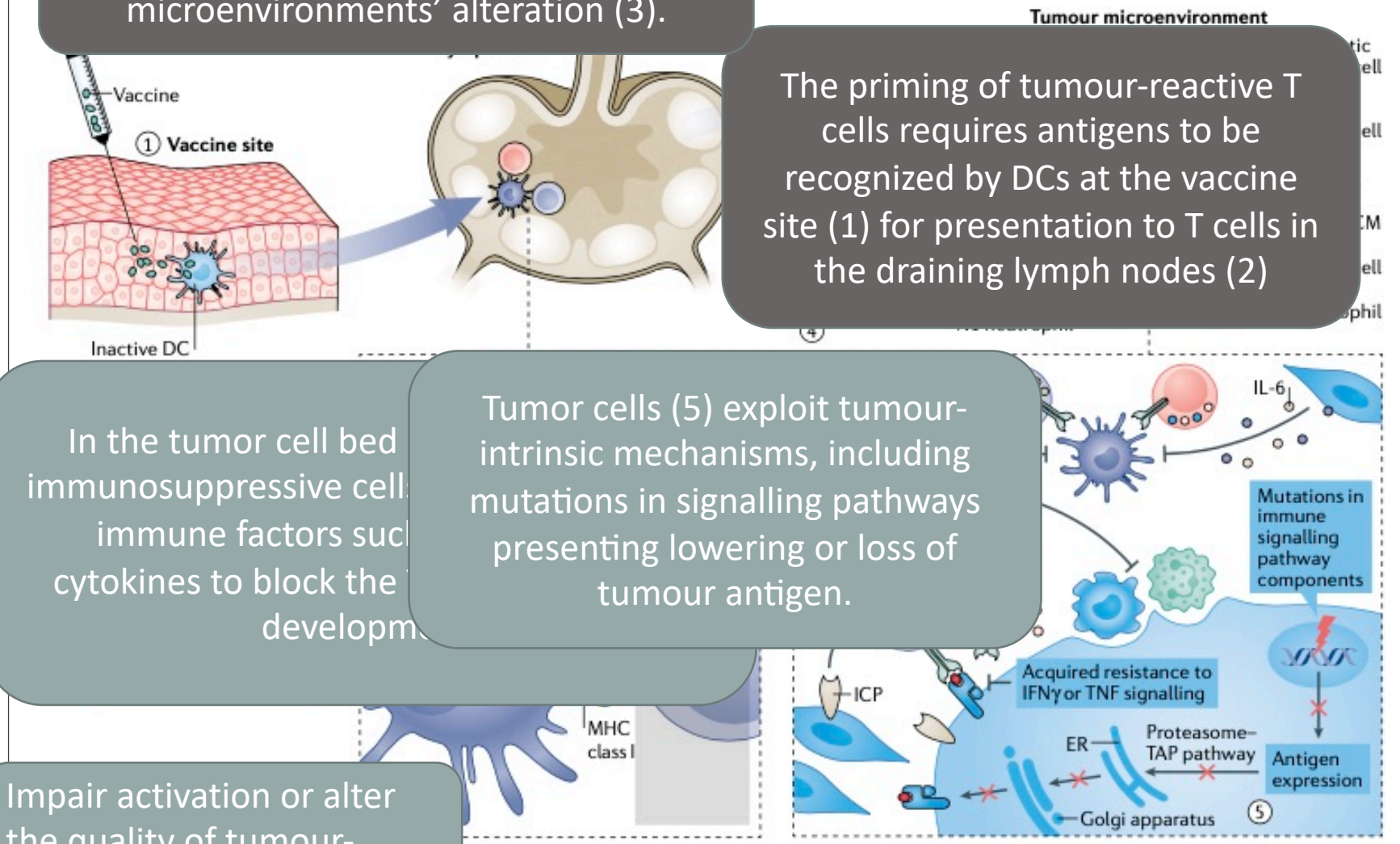
The migration of activated T cells to tumors may be blocked due to the tumor microenvironments' alteration (3).

The priming of tumour-reactive T cells requires antigens to be recognized by DCs at the vaccine site (1) for presentation to T cells in the draining lymph nodes (2)

In the tumor cell bed immunosuppressive cell immune factors suc cytokines to block the develop

Tumor cells (5) exploit tumour-intrinsic mechanisms, including mutations in signalling pathways presenting lowering or loss of tumour antigen.

Impair activation or alter the quality of tumour-reactive T cells.

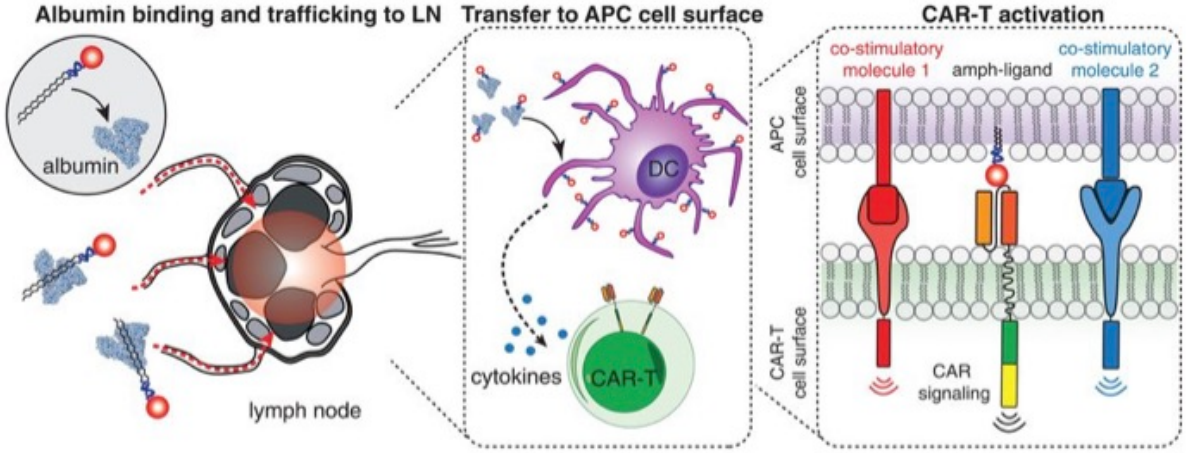


(Saxene, et al., *Nature Reviews Cancer*, 2021)

Some perspectives about Future Cancer Vaccine Development:

- Vaccines are safe and can elicit **long-term immune memory responses, which may be suitable for early-stage or minimal residual disease settings.** (Hollingsworth, & Jansen, *npj Vaccines*, 2019)
- **Identifying antigens** and **vaccine vectors** that will lead to strong and broad T cell responses, tailoring vaccine designs to achieve **optimal antigen presentation** by professional APCs, and finding combination partners to **overcome the diverse cancer immune escape**.
- Therapeutic cancer vaccines may also **help actualize the full potential** of immunotherapies.

eg: CAR-T-related vaccine



(MA, et al., *Science*, 2019)

- Pan-cancer vaccines based on Pan-cancer genome analysis

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THANKS FOR YOUR TIME

Q&A

mRNA-based cancer vaccines in clinical trails

Table 1. Overview of representative mRNA-based cancer vaccine clinical trials

Vaccine type	Antigens and costimulatory molecules	Outcomes	Challenges
Autologous dendritic cell	• TriMixDC-MEL: mRNAs encoding CD70, CD40L, constitutively active TLR4 and tumor antigens (134, 180) • WT-1 dendritic cell: mRNA encoding WT-1 (181) AGS-003: whole-tumor mRNA and synthetic CD40L mRNA (182) • RNA/dendritic cell vaccine: whole-tumor RNA (183)	• Safe toxicity profile • Antigen-specific T cell responses in some patients • Proinflammatory changes in TME observed in some patients	• Costly • Laborious to produce • Variation in patient-specific dendritic cell preparations limiting • Variation in dendritic cell trafficking after injection
Naked mRNA	• TriMix: mRNA encoding CD70, CD40L, and constitutively active TLR4 (184) • IVAC MUTANOME (BioNTech): mRNA encoding personalized neoantigens (4) • mRNA-Mix: mRNA encoding MAGE-A1, MUC1, CEA, and survivin (185)	• Safe toxicity profile, mild adverse events • Antigen-specific T cell responses detected after vaccination in subset of patients • Promising clinical responses in combination with ICB	• Short half-life • Limited uptake in cells • Requires ultrasound-guided injection into lymph nodes
Protamine-coated mRNAs	• RNActive, CV9201: mRNA encoding NY-ESO-1, MAGE-C1, MAGE-C2, survivin, 5T4 (186) • RNActive, CV9103: mRNA encoding PSA, PSCA, PSMA, and STEAP1 (187)	• Safe toxicity profile, mild to moderate adverse events • Activation of T cell responses in small proportion of patients • Significant increase in B cell responses	• Modest immunogenicity
Lipid-complexed mRNAs	• mRNA-2416 (Moderna): mRNA encoding OX40L (188) • mRNA-2752: mRNA encoding OX40L, IL-23, IL-36γ (189) • mRNA-4157 (Moderna): mRNA encoding patient-specific neoantigens (190, 191) • FixVac, BNT111 (BioNTech): mRNA encoding NY-ESO-1, tyrosinase, MAGE-A3, TPTE (5, 152)	• Safe toxicity profile, mild adverse events • Activation of antigen-specific $CD4^+$ or $CD8^+$ T cells in large subset of patients • Proinflammatory changes in TME • Durable disease control for some patients • Promising clinical responses in combination with ICB	• Variable tumor-associated antigen–specific responses in subsets of patients

ICB, immune checkpoint blockade.

(Huff, Jaffee, & Zaidi, *The Journal of Clinical Investigation*, 2022)