CANCER STEM CELL BIOLOGY and CANCER VACCINES
(10)

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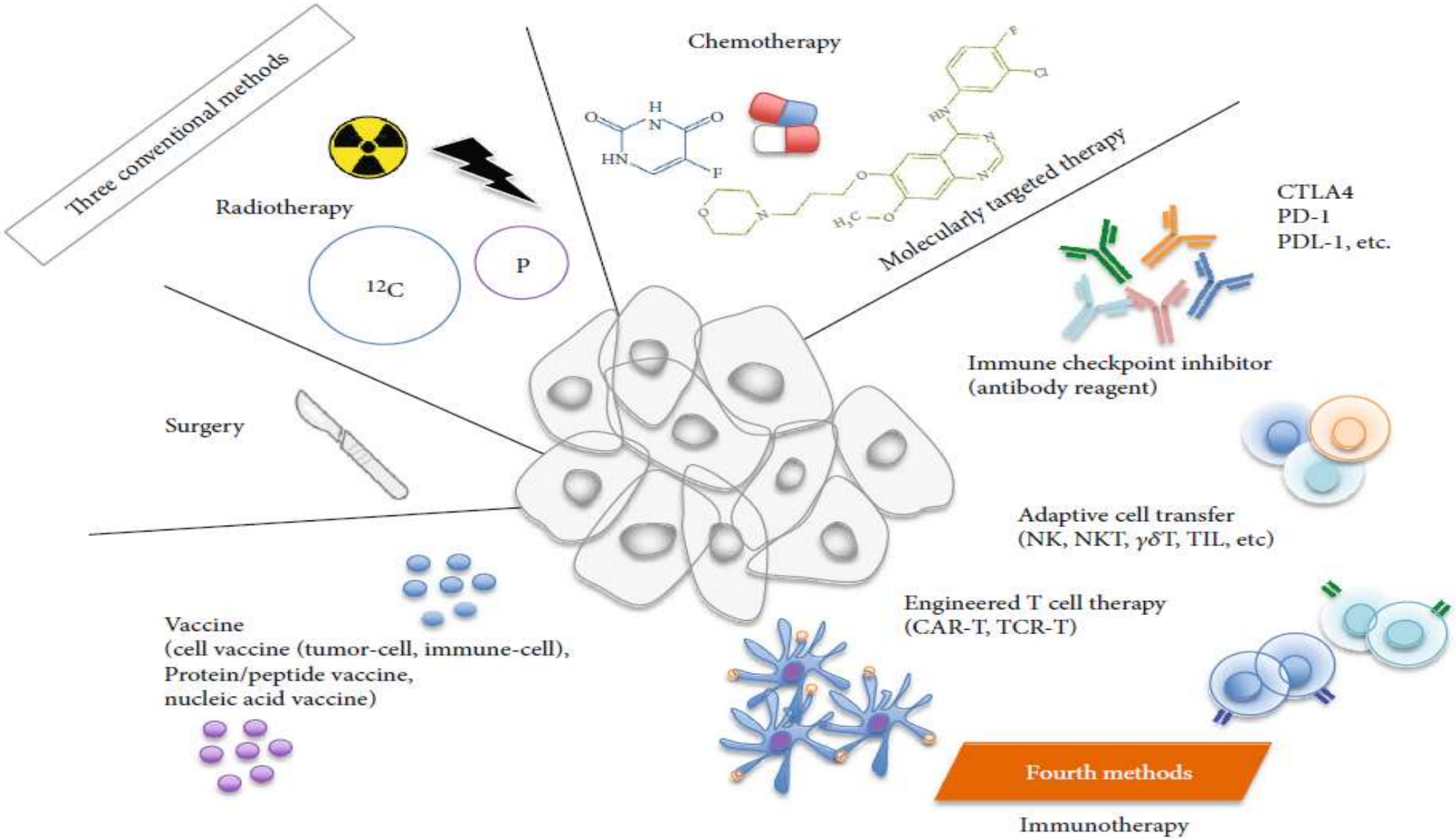
Fall-2021

Cancer Vaccines



Igarashi and Sasada, 2020

Cancer Vaccine History

- Chemotherapy, radiotherapy, and surgical excision are the three major cancer treatment methods that directly remove or target the cancer cells.
- The critical role of TME made the cancer immunotherapies 4th method.

- Preventive and therapeutic vaccines exist as representative strategies for cancer immunotherapy:

✓ The preventive is aimed at inducing immune memory by administering vaccines to healthy persons to prevent morbidity due to a particular cancer.

✓ The therapeutic is administered to patients with cancer for disease management by reinforcing or reactivating the patient's own immune system.

- The Food and Drug Administration (FDA) has approved two types of prophylactic cancer vaccines for targeting the human papillomavirus (HPV) and hepatitis B virus (HBV) to prevent HPV-related cancers and HBV-related hepatocarcinoma.

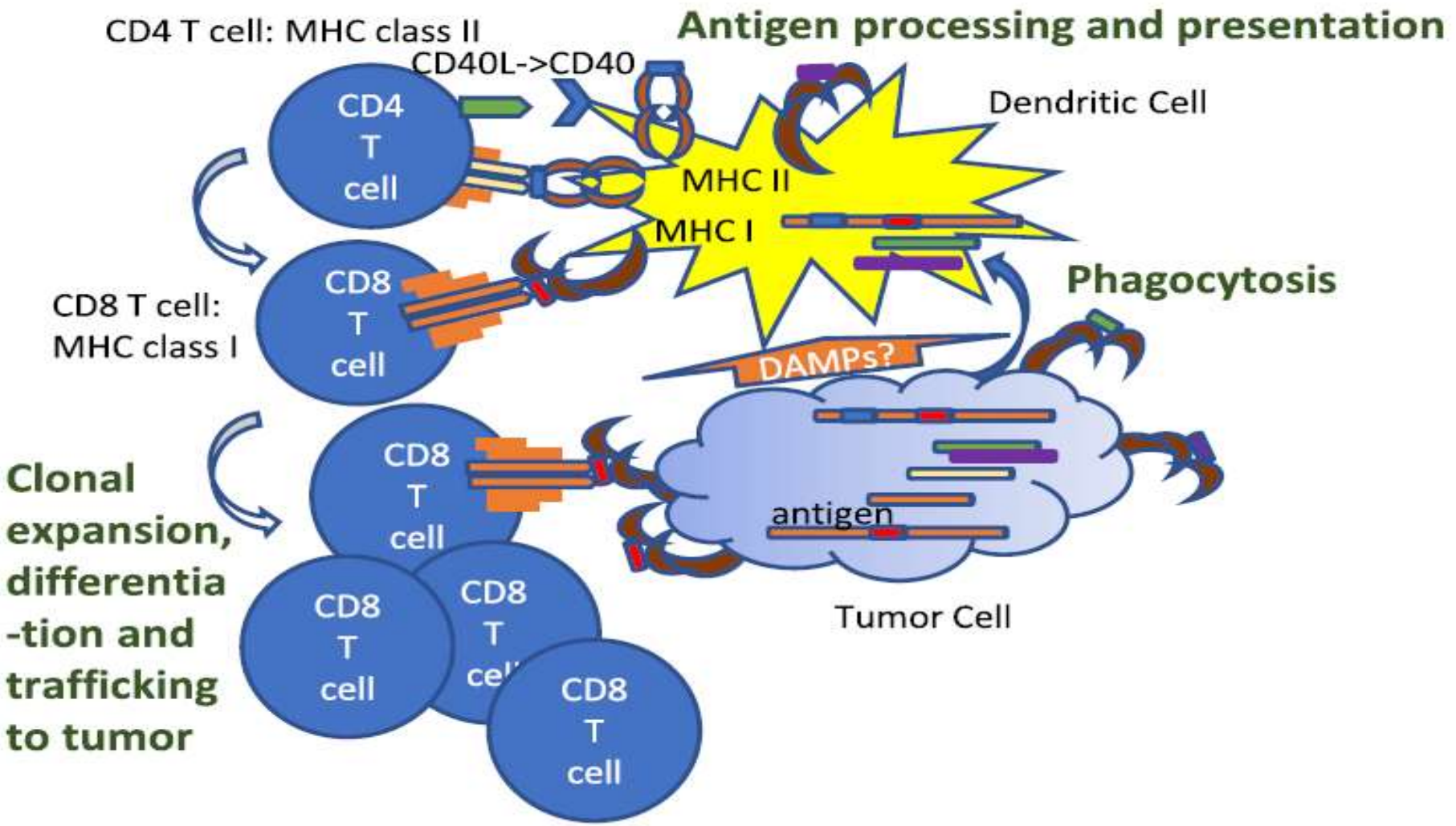
Cancer Vaccine	Strategy	Vaccine Type	Advantages	Disadvantages
Preventive	Viral antigens-based vaccines	HBV HPV (Gardasil, Cervarix)	Highly efficacious Excellent safety profile Highly immunogenic	Restricted to cancers with known etiopathogenic agents
	Retired antigens-based vaccines	AMHR2-ED α-lactalbumin	Specific for adult onset non-viral associated cancers Highly specific Immunogenic	Only applicable to cancer types with known retired antigens
	Embryonic material-based vaccines	Intact ES cells Intact IPSCs ES cell exosomes	Comprehensive immune responses against multiple antigens; Broad spectrum (off-the shelf)	Complex and costly manufacture procedure
Therapeutic	Cell-based vaccines	Gvax Sipuleucel-T Algenpantucel-L STINGVAX	High antigenic immunogenic potency; Control of antigen presentation	Risk for vaccine-triggered adversary effects; Complex and costly manufacture procedure
	Viral vector- or bacterial vector-based vaccines	PROSTVAC ALVAC	High antigenic immunogenic potency; Broad spectrum (off-the-shelf); Suitable for large-scale manufacture	Host-induced immune responses to vectors; Safety concerns for accidental infection; Risk for vaccine-triggered adversary effects
	Peptide-based vaccines	CTAG1B MAGE-A3 BIRC5 WT1 Peptide-based mutant neo-epitopes (personalized vaccines)	Low risk for vaccine-triggered adversary effects; Suitable for large-scale manufacture	Modest antigenic immunogenic potency; Restriction in HLA haplotype subtype
	DNA- or RNA-based vaccines	RNA-based neo-epitopes (personalized vaccines) RNA-based TAAs (NY-EXO-1, MAGE-A3, Tyrosinase)	Flexible to deliver multiple antigens; No restriction in HLA haplotype subtype; Comprehensive T cell and B cell responses; Suitable for large-scale manufacture	Modest antigenic immunogenic potency; Stringent temperature requirements for storage and transport of RNA-based vaccines

Donninger et al., 2021

Cancer Cell Immunologic Behaviour

- The mechanism by which tumors evade the immune system called “cancer immunoediting” as one of the immune evasion tactics utilized by the tumors.

- The interaction between the immune system and cancer cells, which originally contained specific genetic mutations, may cause a selective and biased proliferation of the clones that have lost these mutations, leading to tumor escape from the immune system.

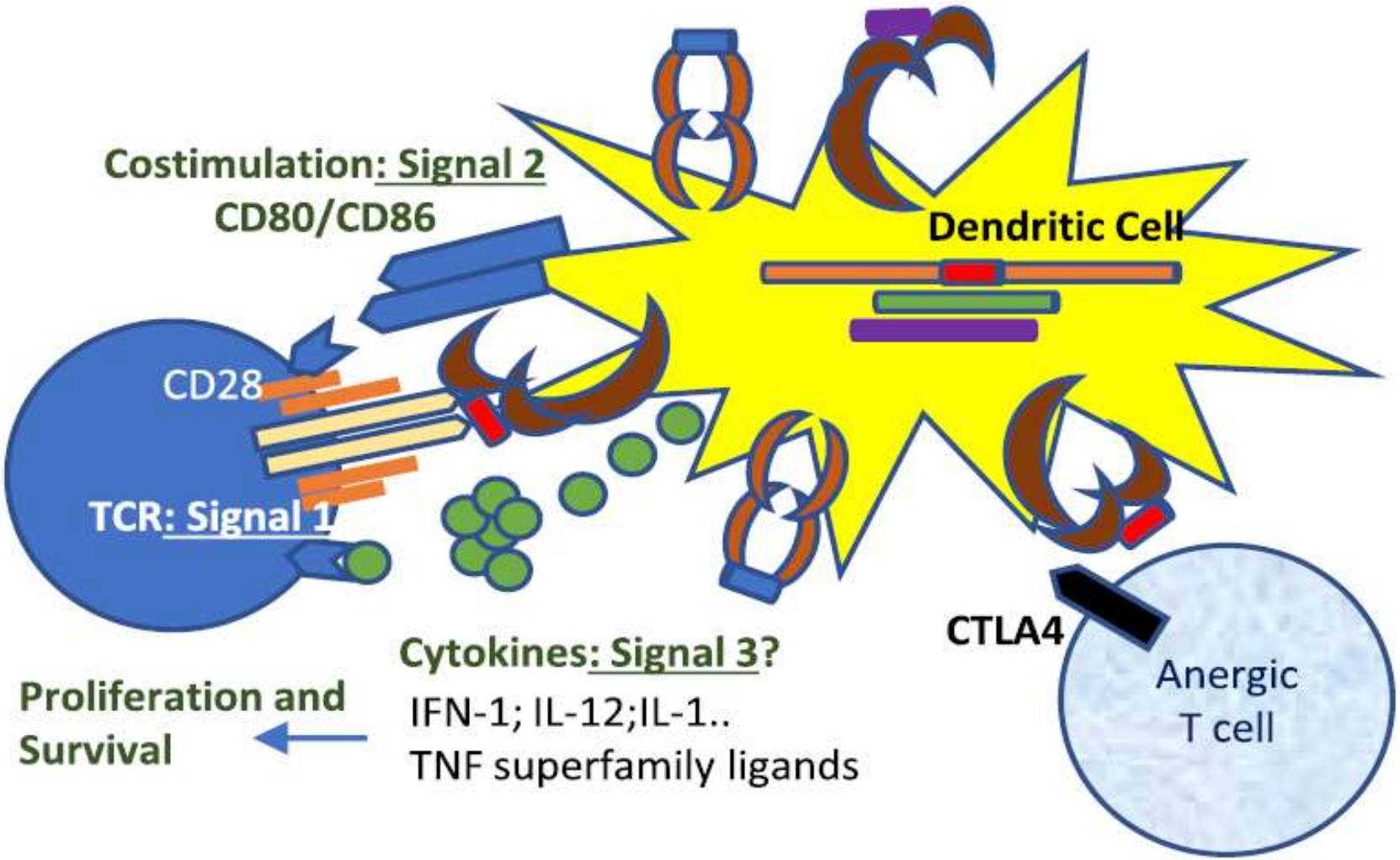


Bullock, 2021

Cancer Cell Immunologic Behaviour

- The presentation of cancer cell antigens to the T cells differs from the presentation of antigens by mature antigen-presenting cells (APCs) in the context of the participation of costimulatory molecules. Antigen presentation by the APCs involves the presence of a simultaneous second signal from costimulatory molecules, such as CD28, for inducing T cell activation during antigen recognition.

- Immunosuppressive cells (e.g., myeloid-derived suppressor cells (MDSCs) and regulatory T (Treg) cells) are recruited to the TME by chemotactic factors derived from tumor, stromal, or other immune cells and convey negative signals to the antitumor immune cells via the expression of inhibitory ligands (e.g., programmed death-ligand 1 (PD-L1)) and the secretion of immunosuppressive factors (e.g., IL-10, TGF-b, and prostaglandin E2 (PGE 2)).



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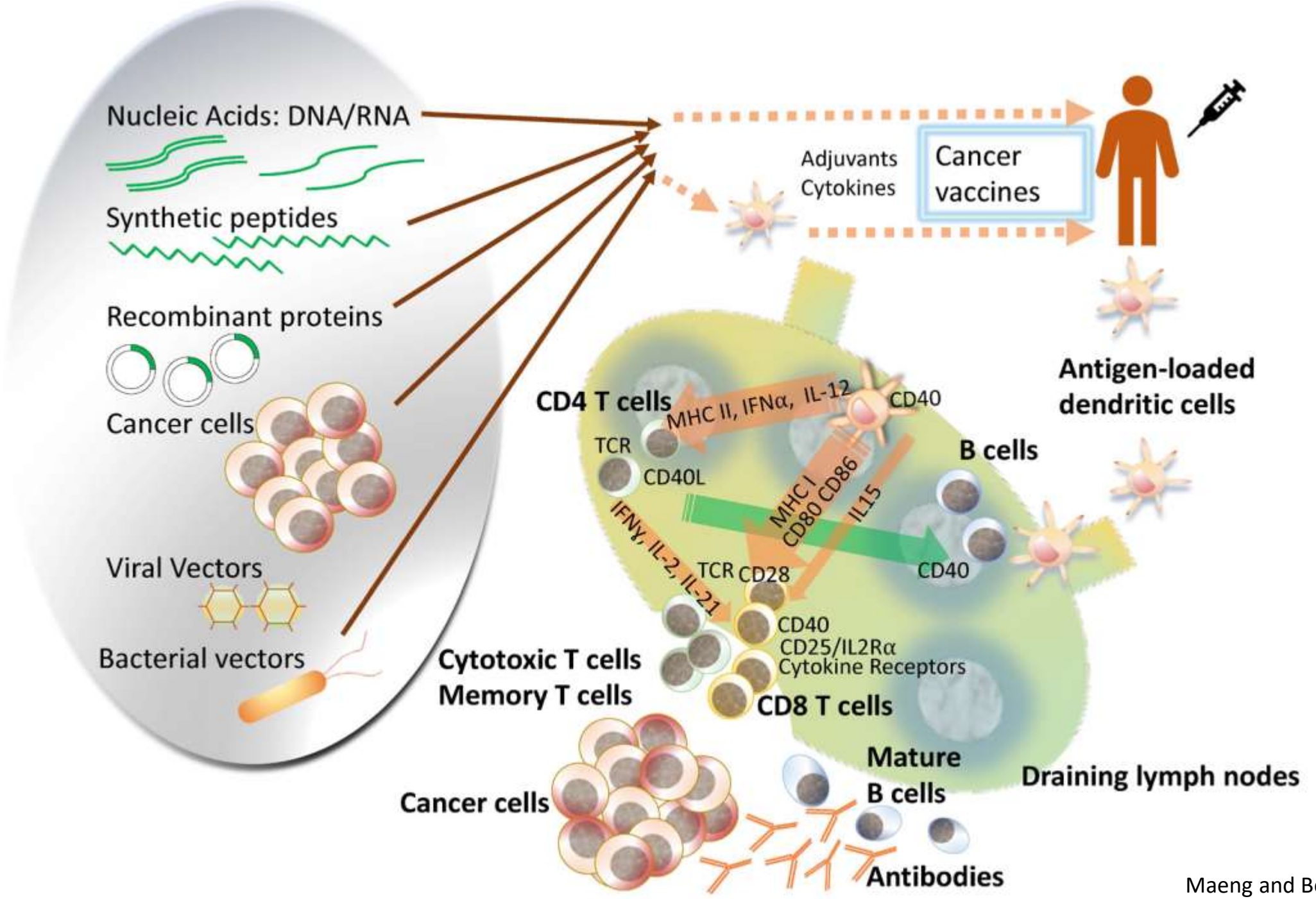


Maeng and Berzofsky 2019

Classification of Cancer Vaccines

1. cell vaccines (tumor or immune cells)
2. protein/peptide vaccines
3. nucleic acid vaccines (DNA, RNA, or viral vector)

1. Cell vaccines (tumor or immune cells)

Tumor Cells

- An **autologous** tumor cell vaccine using a patient's own tumor cells.
- Irradiated tumor cells are administered along with an adjuvant. As this vaccine uses tumor cells, it might be possible to induce T cells specific to any antigen expressed by the used cells. However, the limitation of this strategy is that a sufficient number of cells is sometimes difficult to obtain.
- This approach has been attempted in many tumors, including lung cancer, colorectal cancer, melanoma, renal cell carcinoma, and prostate cancer. In many cases, tumor cells are genetically modified to add functions, such as cytokine production (e.g., IL-2 and GM-CSF) and costimulation (e.g., B7-1).
- GVAX is a cancer vaccine based on tumor cells genetically modified to secrete GM-CSF. It is used after cancer irradiation to stop the uncontrollable growth of cancer cells. There are two types of GVAX vaccine approaches, one using autologous cells (patient-specific), and the other using allogeneic cells (nonpatient- specific).
- GVAX phase 1/2 clinical trials in patients with non-small-cell lung carcinoma have shown good results, correlating GM-CSF secretion and patient prognosis. However, no effects have been seen in phase 3 clinical trials for prostate cancer. Currently, several phase 2 trials of GVAX therapy for advanced pancreatic cancer have been conducted in combination with body radiation or mesothelin-expressing Listeria monocytogenes vaccine or cyclophosphamide (CY), with promising results.

1. Cell vaccines (tumor or immune cells)

Tumor Cells

- An allogeneic tumor cell vaccine that includes tumor cell lines, such as Canvaxin, may overcome the limitation associated with the individualization of autologous tumor vaccines.

- These vaccines have been studied in prostate, breast, and pancreatic cancers.

1. Cell vaccines (tumor or immune cells)

Immune Cells

- DCs that present antigens to T cells and promote immune system activation.
- DC therapy has been intensively studied since the late 1990s, when Dr. Ralph M. Steinman, who discovered DCs, recognized their potential, and the possibility of using DCs as a vaccine.
- A variety of antigens, including tumor cells, tumor-derived proteins or peptides, and DNA/RNA/- virus, could be potentially loaded on DCs. There are additional methods, such as the fusion of DCs with tumor cells.
- Several receptor types are expressed on the surface of DCs. For example, binding of an antigen to a lectin-like receptor known as scavenger receptor on DCs is reported to induce antigen-specific suppressive CD4(+) T cells.
- It is noteworthy that not all antigen presentation by DCs contributes to immune activation.

1. Cell vaccines (tumor or immune cells)

Immune Cells

- In 2010, Provenge (sipuleucel-T; Dendreon Corporation) was approved by the FDA as a prostate cancer vaccine
- It is a leukocyte fraction recovered from the peripheral blood of an individual patient, which is then cultured with a prostate carcinoma antigen (prostatic acid phosphatase (PAP)) in the presence of GM-CSF.
- DCs are the main active components of Provenge (about 11.2%) and display the PAP antigen to artificially stimulate and induce antigen-specific T cells in patients.
- Provenge is a good example of the complexity of personalized medicine, as personalized cancer vaccines can be effectively created using this approach. Nevertheless, all of the processes involved in the production of a personalized vaccine, from sample collection to transporting, processing, shipping, and administration of the cells, need to be customized for each patient, leading to increased labor and cost.

2. Protein/Peptide vaccines

- Protein/peptide vaccines can induce immunity against specific antigenic epitopes derived from the vaccinated protein/peptides that are expressed in cancer cells (and preferably not expressed in normal tissues).

- When an artificially synthesized antigen protein/peptide is administered, it is taken up by professional APCs and presented in complex with the HLA molecules on the cell surface.

- When T cells recognize the antigens, cancer-specificimmune responses are induced. Antigenic epitopes derived from tumor-associated antigens (TAAs) capable of binding HLA have been extensively identified.

- As many early protein/peptide vaccine clinical trials have resulted in favorable results, phase 3 trials have been conducted to confirm the results. Unfortunately, most of these trials have failed, suggesting that single-protein/peptide vaccines do not exert sufficient antitumor effects. These unexpected results may be explained by several factors, including tumor immune escape mechanisms and immunosuppressive TMEs.

2. Protein/Peptide vaccines

- There may be problems with the vaccine formulations; most peptide vaccines developed thus far consist of shortchain peptides (SPs) restricted to MHC class I.

- MHC class I-restricted SPs cannot contribute to the activation of MHC class II-restricted helper T cells, which are important for efficient cytotoxic T lymphocyte (CTL) induction. However, LPs can be processed to both MHC class I- or class II-restricted antigens and presented by professional APCs, but not by other cell types.

3. Nucleic acid vaccines (DNA, RNA or Viral Vector)

- Nucleic acid (DNA/RNA) vaccines have advantages in that they can simultaneously activate immunity against multiple epitopes.

- Further, these vaccines are inexpensive and can be synthesized stably. When an immunogenic viral vector is used, the adjuvants are not as important, unlike in peptide vaccines.

- Developing an efficient delivery method becomes an important issue, especially as the efficiency of nucleic acid uptake into cells might be low.

3. Nucleic acid vaccines (DNA, RNA or Viral Vector)

DNA vaccines

- DNA vaccines have shown promise in several preliminary studies.
- For example, VGX3100, a DNA vaccine for cervical cancer, is in phase 3 clinical trials (NCT03185013).
- Typically, a DNA vaccine is prepared by inserting the gene sequence of interest into a plasmid backbone that needs to be expanded and purified for administration via intradermal, subcutaneous, or intramuscular routes.
- When the plasmid enters the residential APCs or surrounding cells (such as myocytes), transcription occurs, resulting in expression of the protein of interest. The cell machinery provides post-translational modifications to the antigen in a manner similar to that in target cells of the vaccine.
- APCs play a dominant role in the effect of DNA vaccines by presenting the processed peptides on major histocompatibility complex (MHC) class I molecules either from a direct transfection or through cross-presentation of antigens taken up by phagocytosis of transfected cells.

3. Nucleic acid vaccines (DNA, RNA or Viral Vector)

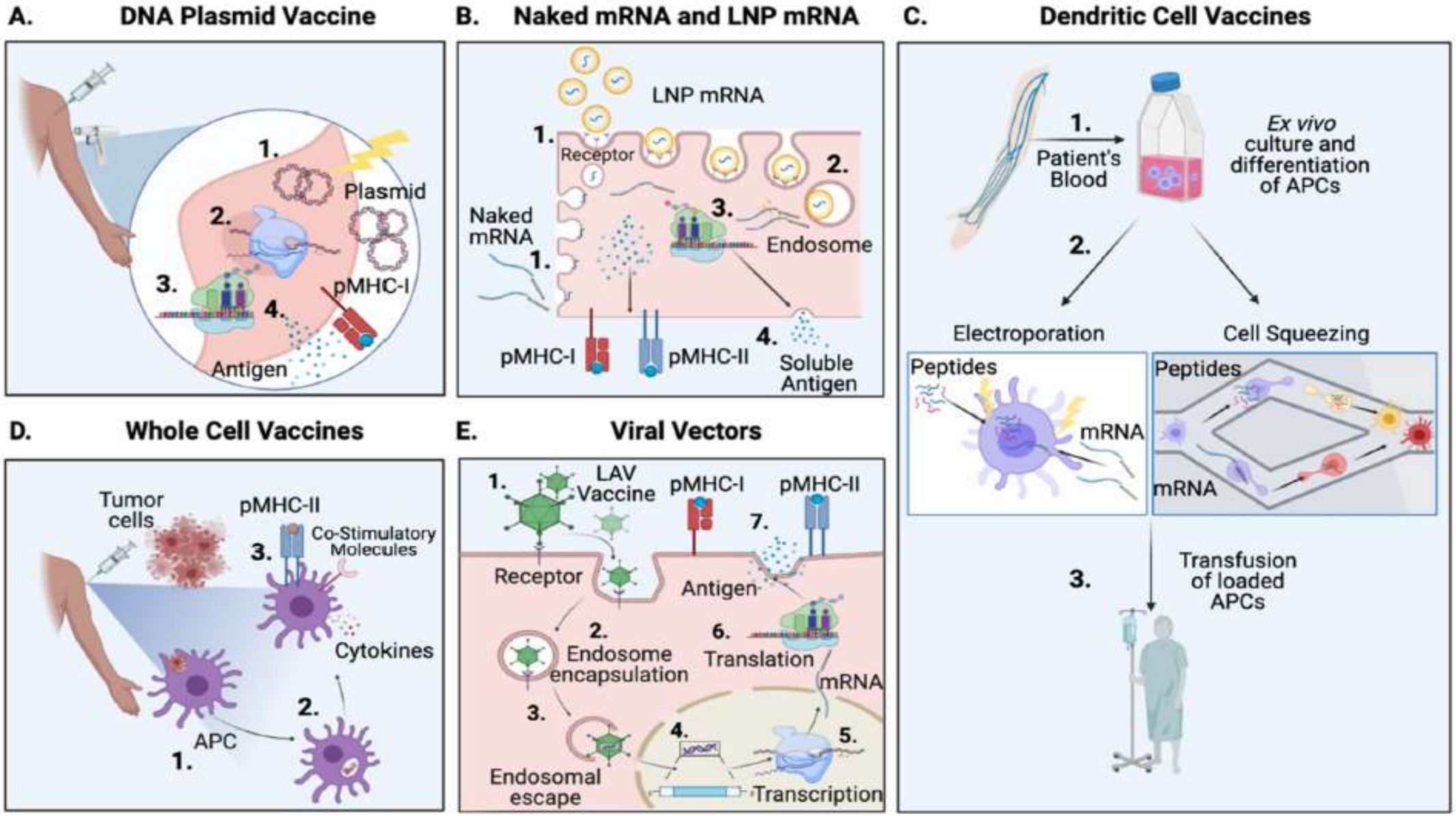
RNA vaccines

- RNA vaccines, unlike DNA vaccines, are not incorporated into the genome, thereby preventing carcinogenicity.
- Unlike DNA vaccines that need to enter the nucleus, RNA vaccines can function in the cytoplasm. Therefore, clearance is quick and the possibility of causing side effects might be low.
- RNA is more easily degraded than DNA, but stability can be enhanced by various modifications, such as formulations with liposomes or stabilizing adjuvants.
- Techniques have also been developed to stabilize the RNA molecule itself (5’ cap structure, untranslated regions, and codon usage in translated regions).
- Phase 1/2 studies are ongoing for melanoma and kidney cancer. A phase I study of liposome-encapsulated mRNA for patients with advanced melanoma is also underway.
- Further development of nucleic acid delivery methods will serve as a breakthrough in nucleic acid vaccines.

3. Nucleic acid vaccines (DNA, RNA or Viral Vector)

Viral vectors

- Viral vectors are used to efficiently carry nucleic acids for vaccines.
- Adjuvants are not required for viral vectors, which can activate innate immunity and also induce immune responses to viruses.
- Commonly used viral vectors are derived from poxvirus, vaccinia virus, adenovirus, and alphavirus and are attenuated or replication-defective for safety.
- The disadvantage of viral vectors is that repeated administration might be difficult due to the induction of antiviral immune responses.



Tay et al., 2021

Vaccine Delivery

- Most vaccines have been studied using a parenteral route, primarily subcutaneous, intradermal, or intramuscular, with less favor for intravenous delivery because of low immune response and concerns about direct organ toxicity or anaphylaxis.

- Intratumoral injection has been studied predominantly in melanoma and brain tumors often with local conditioning with cytokine or toxoid but also in several solid tumors in case of vectors of lytic or direct cytopathic potential.

Vaccine Delivery

- In theory, intravenous infusion of DCs can deliver DCs to secondary lymphoid tissue rapidly and intratumoral injection has an advantage of modulating the TME.

- Intradermal delivery of DCs was most effective in animal models.

- In general, relatively few DCs were detected in the DLNs when they were intradermally or intratumorally administered. Direct injection into a single or multiple lymph nodes did not show any improvement compared with intradermal injection.

Vaccine Delivery

- Overall, the chemical and immunologic nature of the vaccine composition that can result in local tissue damage or altered immunologic cascade should be considered to determine the optimal route and the depth of injection to maximize safety and immunogenicity.

- Vaccine route may also affect the balance between responses of circulating versus tissue-resident memory T cells, as both may be necessary for efficacy.

- The immunologic properties and expected mechanism of immune activation have led investigators to individual choice among subcutaneous, intradermal, intramuscular injection, and intravenous infusion.

Cancer Vaccine + Combination Therapy

- Monotherapies using cancer vaccines often had minimal clinical effects except for certain specific cancer types.

- The relatively low efficacy of monotherapies was attributed to the multifaceted immune evasion mechanisms of cancer, which are difficult to control by either cancer vaccine alone.

- The immunosuppressive TME may override any antitumor effects elicited by the cancer vaccine.

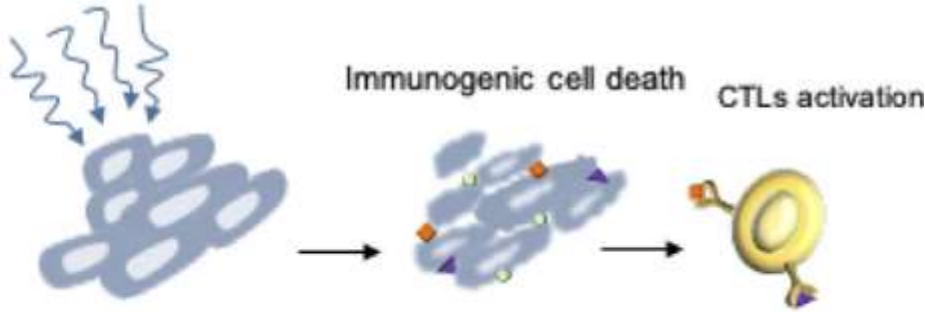
- In accordance with the development of various immunotherapy types, more attention has focused on combination therapies. Several different approaches, including conventional chemotherapy/radiation therapy or the latest antibody therapies, have been attempted in combination either simultaneously or in sequence with immunotherapies.

Combo of vaccine adjuvants

Effective expansion of immune cell types

- Prevention of Ag degradation
- APCs activation
- Induction of CTL and memory T cells
- Use of immuno-stimulatory cytokines

Radiotherapy (abscopal effect)



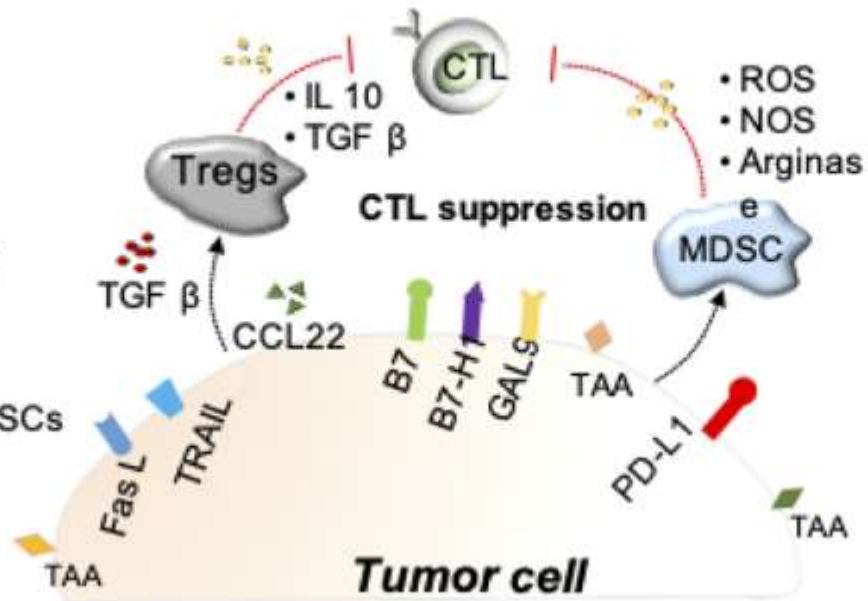
Tumor irradiation - Release of stimulatory molecules (death receptors, Fas, adhesion molecules)

Improved cancer vaccine efficacy

Chemotherapy

Targeting reduction/depletion of immuno-suppressive cells

- Cyclophosphamides –Tregs
- Platinum salts, taxanes, 5FU - MDSCs



Immune checkpoint inhibitors

Improving interactions between tumour and immune cells

- PD-L1 inhibitors
- PD1, CTLA4, TIM3, LAG3 inhibitors
- Stimulatory molecule agonist for T cell activation (OX-40, 4-1BB, ICOS etc.)

Cuzzubbo et al., 2021

Conclusion

- During the past 30 years of modern cancer vaccine development, various vaccine platforms have been tried in clinics.
- Sources of tumor antigen can be synthetic (nucleic acids or peptides), viral, or microbial vectors or autologous or allogeneic tumor cell–derived cells, tumor cell lysates or RNA.
- Some platforms use infectious organisms to present the tumor antigen to APCs *in vivo*, whereas some researchers use DCs *in vitro* for antigen loading.
- Costimulatory molecules and cytokines have been tried, but no clear consensus has been made on the optimal choice.
- Vaccine adjuvants has been developed by a National Cancer Institute working group.
- The majority of the vaccines that were successful in inducing immunologic anti-tumor response could not match that success in the clinical response, indicating the need for improved vaccine platforms and probably combinations with checkpoint inhibitors or other methods to block immune suppression by cancer.

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