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AMPLIFIED REVIEW REFLECTING THE SIGNIFICANCE OF THERAPEUTIC CANCER VACCINES

Aliya Parveen* [1], Amtullah Amena Ahmed [1], Rumaisa Saher[1], Arshee Banu [1], Mehjabeen [1] Syed.Azizullah Ghori [2]

[1]Pharm. D, [2]Department of Pharmacy Practice, Deccan School of Pharmacy, Darussalam, Hyderabad - 01, A.P.

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***Correspondence for Author**
Dr. Aliya Parveen
Pharm. D, Department of Pharmacy Practice, Deccan School of Pharmacy, Darussalam, Hyderabad - 01, A.P

ABSTRACT

Cancer is a group of disease characterized by abnormal, excessive, uncoordinated, autonomous and purposeless proliferation of cells. In spite of significant development in the cancer therapy, it is one of the leading causes of death worldwide. According to American Cancer Society in 2014, there will be an estimated 1,665,540 new cancer cases diagnosed and 585,720 cancer deaths in the US. According to International Agency for Research on Cancer (IARC), Part of WHO effective preventive measures like vaccination, diet etc. are the only way to prevent cancer crisis. About 50% of the cancer cases can be reduced by vaccination alone. Cancer vaccines are the biological preparations that are used to prevent the cancer in high risk individuals (preventive vaccines) or to treat the disease that already exists (Therapeutic Vaccines). These vaccines aim to recognize the antigens expressed in tumor cells and destroy them leaving the normal cells intact by priming Ag-specific T cells and reprogramming memory T cells. Research in molecular biology and immunology has resulted in the development of a range of recombinant vaccines viz., antigen, tumor cell, anti - idiotype antibody-based, dendritic cell-, DNA-, and viral- vector based- vaccines. Cancer vaccine are ineffective due to immunological barriers like mutations and tolerance, lack of awareness, inappropriate choice of tumor antigen or unoptimised antigen delivery system or vaccination schedule or selection of wrong patient group. More research is required to overcome the potential limitations of vaccines. These new vaccines along with those in use may substantially reduce the global mortality from cancer and proveto be a savior to mankind.

KEY WORDS: Cancer Vaccines, Recombinant vaccines, Immunological Barriers, Therapeutic Vaccines, IARC.

INTRODUCTION

Cancer is a group of disease characterized by abnormal, excessive, uncoordinated, autonomous and purposeless proliferation of cells.

The Hallmarks of Cancer Include

1. Excessive and autonomous growth: Growth promoting oncogenes
2. Refractoriness to growth inhibition: Growth suppressing anti-oncogenes.
3. Escaping cell death byapoptosis: Genes regulating apoptosis and cancer.
4. Avoiding cellular aging: Telomeres and telomerase in cancer.
5. Continued perfusion of cancer: Cancer angiogenesis.
6. Invasion and distant metastasis: Cancer dissemination.
7. DNA damage and repair system: Mutator genes and cancer.
8. Cancer progression and tumor heterogeneity: Clonal aggressiveness.[1]

In spite of significant progress in the development of cancer therapy like radiation therapy, chemotherapy, angiogenesis blockers, and stem cell therapy etc. Cancer is one of the leading causes of death world-wide. The International Agency for Research on Cancer (IARC) – part of the World Health Organization – predict that new cancer cases will rise to 19.3 million per year by 2025. There were also 8.2 million cancer-related deaths last year, compared with 7.6 million five years ago. A global focus on cancer preventioni.e. vaccination and screening tests etc. will be needed to help stem the continued rise in cancer cases around the world, an international organization reports.

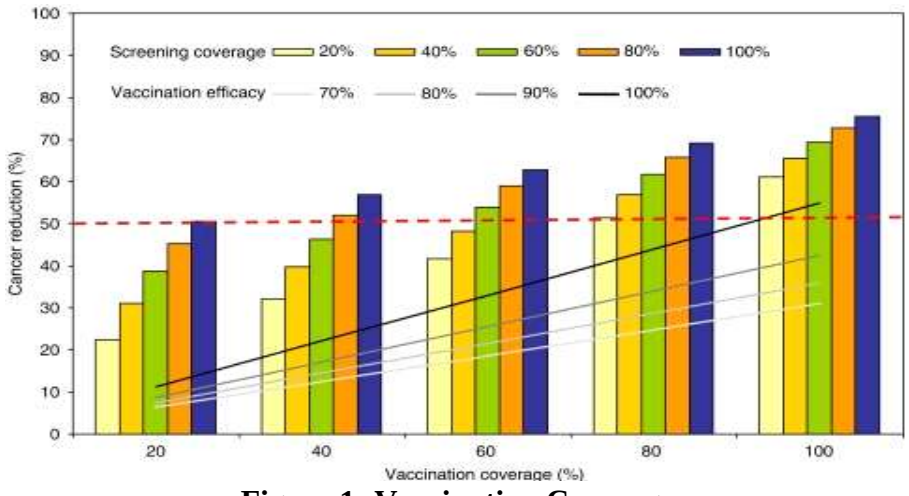


Figure 1: Vaccination Coverage

The above Graph plotted between the cancer reduction on y axis and vaccination on x axis depicts the impact of vaccination coverage on cancer reduction. The colored bars represent different coverage levels of vaccine efficacy (white, 70%; light grey, 80%; dark grey, 90%; black, 100%). The dashed red line represents a threshold of 50% cancer reduction. [2]

Cancer Vaccines

Cancer vaccine is a Biological preparation used to prevent or Treat the disease that already exists in contrast to the traditional vaccines that are used to prevent the occurrence of the disease.

Types of Cancer Vaccines

Preventive (Or) Prophylactic Vaccines: These are the vaccines used to prevent the occurrence of the disease in healthy and high risk individuals.

FDA approved cancer preventive vaccines include

1. Gardasil for the prevention of cervical, vaginal and vulvar cancers in girls and women aged 9 to 26.
2. Cervarix for the prevention of cervical cancer in girls and women's aged 10 to 25.
3. Hepatitis B vaccine to prevent infection with HBV (Hepatitis B Virus) whose long lasting infection leads to hepatocellular carcinoma.

Therapeutic (Or) Treatment Vaccines: These are the vaccines used to treat the existing cancer by boosting the body's immune system in patients with early stages of cancer.

FDA approved cancer treatment vaccines include

1. Sipuleucel-T(Provenge®)vaccine for asymptomatic or minimally symptomatic metastatic castrate resistant prostate cancer.[3]
2. Fig.2 Mechanism of action of different cancer vaccines should come first followed by (A)gene modified tumour vaccines,(B)Whole cell tumour vaccine and so on; (C) bacillus Calmette-Guérin (BCG); (D) peptide epitope immunization, recombinant viral vector immunization, and heat shock proteins; (E) naked DNA immunization; (F) immunocytokines; and (G)Human Leukocyte Antigen HLA-B7 intratumoral plasmid injection.

3. All these vaccines lead to the release of tumor antigens which are picked up by professional Antigen Presenting Cells (APCs)called dendritic cells which circulate in the afferent lymph nodes and activate the T cells.
4. These vaccines boost the immune system to produce strong and specific immune response against the cancer cells sparing the host cells.

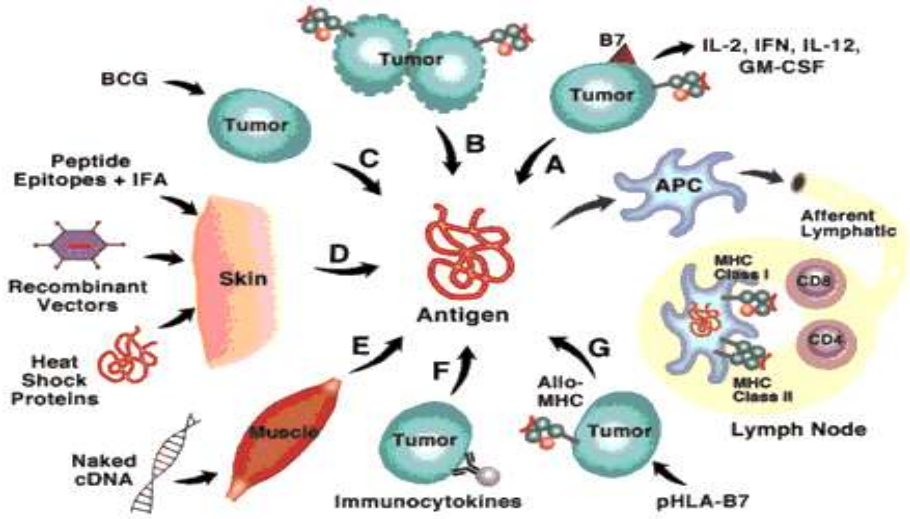


Figure 2: Mechanism of action of Different Vaccines [4]

Table 1: Potential Targets for Cancer Vaccines [5]

Antigen Type	Antigen	Neoplasia
In Table 1: Potential Targets for Cancer Vaccines, Ag = antigen; NHL = non-Hodgkin's lymphoma; CML = chronic myeloid leukemia. Should b at the bottom of the table 1		
Tissue-specific Ag	Prostate-specific Ag	Prostate cancer
	Prostate-specific membrane Ag	Prostate cancer
	Tyrosinase	Melanoma
	Gp100	Melanoma
	α-fetoprotein	Liver cancer
Tumor-specific Ag	Immunoglobulin idiotype	B-cell NHL, myeloma
	TCR	T-cell NHL
	Bcr-abl fusion product	CML
	Mutant p53	Lung, colorectal, head and neck cancer, etc.
Cancer testis Ags	MAGE-1, MAGE-3	Melanoma, lung, and colorectal cancer
	NY-ESO-1	Melanoma and breast cancer
Overexpressed Ags	Her-2/*neu*	Breast, lung, and ovarian cancer
	Muc-1	Pancreatic, lung, breast, and colorectal cancer

Properties of Ideal Cancer Vaccine

The properties of an ideal cancer vaccine include

1. Simple formulation,

2. Easy to manufacture,
3. Stable over a range of ambient temperatures,
4. Conveniently administered,
5. Readily transported,
6. Able to provide lifelong immunity against a given pathogen,
7. Inexpensive.[6]
8. Capable of producing strong and specific anti-tumor response against the cancerous cells sparing the host cells.
9. Capable of producing quick and specific immune response by producing antigen specific memory cells.

Advantages of Cancer Vaccination

1. Used to prevent or treat the disease in healthy and high risk individuals.
2. Cancer cells suppress the immune system vaccines can be used to boost the immune system.
3. Therapeutic vaccines could be combined with chemotherapy, radiation therapy etc. for more significant outcomes.
4. Used to produce strong and specific immune response against tumor cells.
5. Cancer vaccines help to distinguish between the self-antigen and the Tumor Associated Antigens (TAA) present on the surface of cancerous cells and prevent cancer.
6. Treatment vaccines can be used in patients diagnosed with cancer to prevent the cancer from coming back, destroy the cancerous cells remaining in the body, or to stop a tumor from spreading.[7]

Different Types of Cancer Vaccines

Dna Vaccine: These are the genetically engineered DNA vaccines containing plasmids. These plasmids are transfected by the Antigen Presenting Cells (APCs).These APCs stimulate the T and B Cells. In this way the DNA vaccines produce both cell mediated and humoralimmunity.DNAis responsible for genetic coding and synthesis of proteins and can instruct the cells to make specific antigens against the specific cells.

Example: Human telomerase reverse transcriptase (hTERT) is a DNA vaccine target in cancer immunotherapy. High levels of hTERT have been detected in more than 85% of all human cancers, while normal cells showed undetectable levels of telomerase expression.

Multiple cancers expressing the antigen hTERT, include non-small cell lung carcinoma, breast cancer, melanoma, and prostate cancer. [8]

Table 2: Different routes of administration and indication of DNAvaccines: [9]

ROUTES OF ADMINISTRATION	INDICATION
Intramuscular	Prostate cancer and B Cell lymphoma
Intradermal	Prostate and Colon cancer
Tattoo perforating needle	Melanoma
Intratumor	Melanoma and Renal carcinoma
High Pressure	B cell lymphoma
Liquid delivery	Colon Cancer

Heat Shock Protein Vaccines

Heat Shock proteins or the stress proteins are present in normal individuals and are expressed during elevated temperature and stress.

1. Selected HSPs, also known as chaperones, play crucial roles in folding/unfolding of proteins, cell-cycle control and signaling, and protection of cells against stress/apoptosis and present tumor antigens to APCs and in turn leads to anti-tumor activity by inducing specific and non- specific cellular immune responses.
2. Eg: Oncophage, AntigenicsInc, Woburn, MA Javelin, Mojave Therapeutics, Hawthorne, NY; Oncocine HspE7, Stressgen Biotechnologies Corp, Victoria, BC, Canada.

Dendritic Cell Vaccines [10]

Dendritic cells (DCs) are the APCs that play an important role in the activation of naive CD4+ and CD8+T cells.

DCs are induced ex vivo from peripheral blood monocytes, matured, pulsed with tumor antigens and finally administered to patients to produce active immune response.

Recently, the dendritic cells are pulsed with tumor lysates: E.g. DCVax- Lung and DCVax-Brain for Lung and Brain Cancer.

Dendritic cell-tumor cell hybrids, genetically modified dendritic cells and the dendritic cells transfected with tumor-derived messenger RNA are the most recent advances in the dendritic cell vaccines.

Table 3: Dendritic Vaccines against Cancer.

DC Vaccines against Cancer				
Vaccine Approach	**Adjuvant or treatment**	**Target Disease**	**Outcome**	**References**
Ex vivo derived DC given s.c.	Maturation cytokine cocktails, pulsed with tumor antigen	Various cancer types	Improved tumor rejection	[52, 53, 118]
Ex vivo derived DC.	Transduced to express cytokines	Melanoma, glioma	Improved Th1 response	[44, 119–121]
Irradiated tumor cells	Transduced to express cytokines	Various cancers	Increased DC migration and maturation	[46, 122]
Ex vivo derived DC	Transduced to express tumor antigen	Melanoma	Improved Th1 response	[45, 123]
Ex vivo derived DC	Express tumor peptide coupled to MHC class I tracking signals	Lymphoma	Enhanced T cell response and tumor rejection	[86]
In vivo targeting with peptide coupled to anti-CD205 mAb	Poly I:C	Survivin	Strong Th but no CTL response	[96]
In vivo targeting with VLP	Contained tumor antigen HER2Neu	Breast cancer	Prevention of tumor outgrowth	[124]
DC derived exosomes	None	Pancreatic cancer	Activate NK cells	[125]

Anti-Idiotype Vaccines

Antibodies are proteins and can be antigens for other antibodies.

An anti-idiotypic antibody is an antibody against an individual structural determinant of variable region of other antibodies. Vaccines using these types of monoclonal antibodies are called anti-idiotype vaccines.

No adjuvants are needed since the cascade of anti-antibodies ensures a strong and long-lasting immune response.

Racotumomab has been approved in two countries, Argentina and Cuba, for the treatment of recurrent or advanced NSCLC (Non-Small Cell Lung Cancer) Racotumomab is an Monoclonal antibody monoclonal antibody that mimics NGcgangliosides, thus triggering an immune response against the tumor antigen NGcGM3 which is highly expressed in human cancerous cells.

WHOLE CELL CANCER VACCINE:

Whole cell containing tumor antigens can be autologous (taken from the patient) or allogeneic (from the different patient) and are injected together with powerful immunologic adjuvants or haptensto present the tumor antigens in inflammatory context to attract host APCs.

The advantage of tumor cell vaccine is that they do not need to be identified.

The disadvantage of tumor cell vaccine is that both autologous and allogeneic

vaccine have limited ability to stimulate immune system so they are formulated as

Tumor lysates (contain fragments of dead tumor cells),
Tumor cell oncolysates (cancer cells infected with the strains of virus),
Transduced tumor cells that have been genetically engineered to include genetic material from proteins and cytokines that stimulate the immune system.
Whole-cell cancer vaccines: Melacine, Corixa Corp, Seattle, WA; Cancvaxin, CancerVax Corporation, Carlsbad, CA; OncoVax, Intracel LLC, Frederick, MD; MVAX, AVAX, Overland Park, KS; ONYCR1-3, ONYVax, London, UK; CMVAC.

Antigen Based Vaccine or Peptide Based Vaccines:[11]
These vaccines contain specific antigens that are specific to different types of cancer tissues in contrast to the whole cell vaccines that contain more than one antigen. This results in a more specific, memory cell response with limited chance of inducing autoimmunity and reoccurrence of cancer. Tumor Specific Antigen (TSAs) are expressed only by cancer cells and TAAs are expressed at the mutated counterparts of proteins by normal tissues.TAAs can be divided into

UNIQUE TAAs- These are the products of mutations induced by physical or chemical carcinogens and are uniquely expressed in tumors and not by normal tissues.
SHARED TAAs- They can be divided into-
Differentiation antigens
Overexpressed antigens
Cancer testis (CT) antigens
Unsatisfactory results may be due to immune tolerance induced by shared TAAs and limited cytotoxic T-lymphocyte (CTM) expansion due to activation of regulatory t- lymphocytes these limitations can be overcome by using inflammatory cytokines like alpha-interferon (INF-alpha), interleukin-2 (IL-2).

Carbohydrate Based Anti-Tumor Vaccine
Tumor associated carbohydrate antigens (TACAs) which are excessively or uniquely expressed on the cancer cell surface and correlate the different stages of cancer. TACA-based cancer vaccines do not elicit T-cell response in cancer patients and none has been approved for clinical use yet.

Viral Vector Based Vaccine [12]
The term 'vector' refers to an agent that can deliver DNA or antigen into a desired cell type.
.The common vectors used in the development of vaccines are yeasts, bacteria, and viruses. A variety of genetically modified vectors have been adopted to cancer immunotherapy include recombinant incompetent viral vectors (adenovirus, retrovirus,lentivirus).These viruses are incapable of self- replication into infectious progeny virions after infection of a single target cell, but that efficiently express the foreign gene inserted in the vector.

Table 4: Viral Vectors and Cancer Immunotherapy

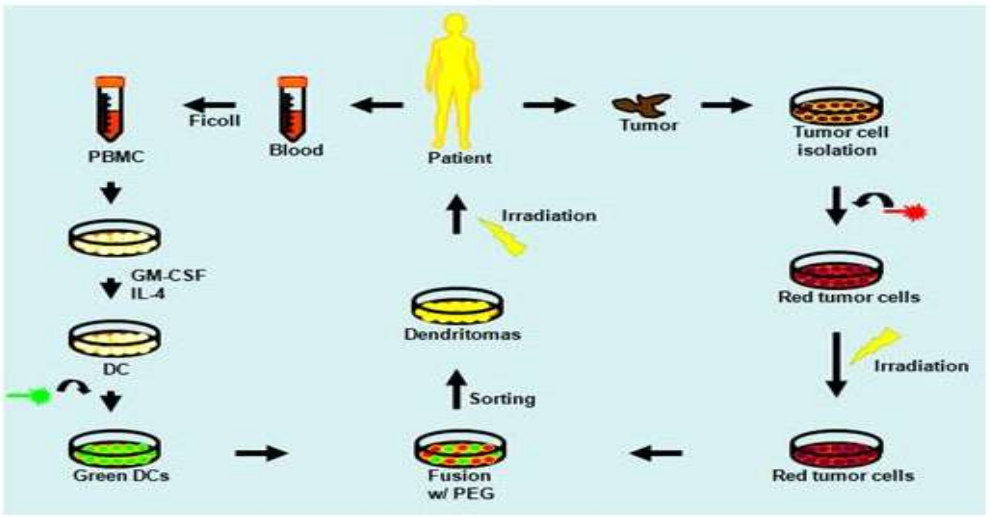
DC – Dendritic cells

CAR – Coxsackie and adenovirus receptor

Examples: Ad-sig-hMUC-1/ecdCD40L vaccine for metastatic breast cancer; alpha fetoprotein adenoviral vector vaccine for liver cancer.

Gene Modified Tumor Vaccine

Gene-modified tumor vaccines are usually composed of autologous tumor cells stably transfected with an immunostimulatory gene.



The paracrine expression of cytokines such as IL-2 or IFNγ, or the costimulatory molecule B7.1, would allow the tumor cell to provide all of the signals for direct cytotoxic T cell activation, bypassing the need for host APCs and $CD4^+$ T lymphocyte help.

These cytokine-modified autologous tumor cell vaccines, tumor cell cultures and collection of cells that adequately express the transgene (may take months). Use of allogeneic gene-modified tumor cell vaccines, transfection of autologous noncancerous cells,viral vectors with enhanced transduction efficiency decrease vaccine production time.

GVAX, GenesysInc, Foster City, California.[13]

Tumor-Apc Hybrids

These hybrids are produced by exposing tumor cells and APCs to polyethylene glycol (PEG) or electrical fields. This results in specific TAA from the tumor cells and co stimulatory properties of the APCs.

Figure 3: The general scheme of tumor APC hybrid vaccine therapyFicoll is used for the separation of PBMC (Peripheral Blood Mononuclear Cells) from the whole blood, GM-CSF (Granulocyte Macrophage Colony Stimulating Factor) IL-4(Interleukin -4), DC (Dendritic Cells), PEG (Poly Ethylene Glycol).

Table 4 viral vectors and chemotherapy

Viral Vector	Advantages	Disadvantages
Adenovirus (Ad)	Easily manipulated in laboratory setting Cellular and humoral immune response to transgene High expression of transgene Broad tropism(specificity of virus to particular host tissues)including DC No risk of insertional mutagenesis Many strains available	Infection of target cells dependent on express of Ad receptor (e.g. CAR), which is not expressed on all cancer cells Pre-existing host neutralizing antibodies to several Ad serotypes Limited capacity for gene inserts
Measles Virus(MV)	Specificity for tumor cells Oncolytic virus No risk of insertional mutagenesis Vaccine strain non-pathogenic, non-contagious	Contraindicated in severely immunocompromised patients Modest capacity for gene inserts
Vesicular stomatitis virus	Broad tropism, including DC High efficacy of gene expression No risk of insertional mutagenesis Vaccine strain non-pathogenic, non-contagious Oncolytic virus	Neurotropsim of concern Modest capacity for gene inserts Viral transgene expression limited by lysis of target cell
Viral Vector	**Advantages**	**Disadvantages**
Adenovirus (Ad)	Easily manipulated in laboratory setting Cellular and humoral immune response to transgene High expression of transgene Broad tropism(specificity of virus to particular host tissues)including DC No risk of insertional mutagenesis Many strains available	Infection of target cells dependent on express of Ad receptor (e.g. CAR), which is not expressed on all cancer cells Pre-existing host neutralizing antibodies to several Ad serotypes Limited capacity for gene inserts
Measles Virus(MV)	Specificity for tumor cells Oncolytic virus No risk of insertional	Contraindicated in severely immunocompromised patients

	mutagenesis Vaccine strain non-pathogenic, non-contagious	Modest capacity for gene inserts
Vesicular stomatitis virus	Broad tropism, including DC High efficacy of gene expression No risk of insertional mutagenesis Vaccine strain non-pathogenic, non-contagious Oncolytic virus	Neurotropsim of concern Modest capacity for gene inserts Viral transgene expression limited by lysis of target cell

Table 5: List of Cancer Vaccines That Are Being Approved From 2000 – 2013

Product Approved	Company	Region	Approval Year	Cancer Type Treated	Vaccine Type
Cervarix	GlaxoSmithKline	European Union	2007	Cervical	Prophylactic
Cervarix	GlaxoSmithKline	United States	2009 (October)	Cervical	Prophylactic
DCVax-Brain	Northwest Biotherapeutics	Switzerland	2007 (November)	Brain	Therapeutic
Gardasil	Merck	United States	2006 (June)	Cervical	Prophylactic
Gardasil	Merck	European Union	2006 (September)	Cervical	Prophylactic
Melacine (disc.)	Corixa Corp	Canada	2001	Melanoma	Therapeutic
MVAX	AVAX Technologies	Switzerland	2005	Melanoma	Therapeutic
MVAX (disc.)	AVAX Technologies	Australia	2000	Melanoma	Therapeutic
Oncophage	Antigenics	Russia	2008 (April)	Renal	Therapeutic
Onco VAX	Vaccinogen	Netherlands	2008 (May)	Colon	Therapeutic
Provenge	Dendreon	United States	2010 (April)	Prostate	Therapeutic

Table 6: Vaccines under Clinical Trial According To Type of Cancer.

Cancer Type	No. of Vaccines under Clinical Trial
Prostate	6
Lung	4
Melanoma	3
Renal	3
Cervical	2
Breast	1
Colon/Rectal	1
Genital Warts	1
Lymphoma	1
Vaginal	1
Vulvar	1

Table 7: Potential barriers to cancer vaccine: tumors escape the immune system.

1. Tumor cells escape CTL recognition
a. Loss of antigen expression
b. Loss, down modulation, or mutation of restricting MHC molecule
2. Inefficient APCs
a. Decreased or lack of expression of costimulatory molecule
b. Cytokine-induced blockade of APC maturation and differentiation (IL-10, transforming growth factor β)
3. Tumors produce immune-suppressive factors (VEGF, IL-10, TGF-β etc.)
4. Tumor-related alterations in T-cell signaling
5. Tumor-induced immune deviation (Th1 → Th2)
6. Majority of tumor antigens are self-antigens, leading to tolerance
7. Cytokine environment at tumor site does not support T-cell expansion
CTL = cytotoxic T lymphocyte; MHC = major histocompatibility complex; APCs = antigen-presenting cells; IL-10 = interleukin-10; TGF-β = transforming growth factor β; VEGF = vascular endothelial growth factor.

Table 8: Dose, Indications, and Side Effects of different Cancer Vaccines. [14-17]

Cancer vaccine	Indication	Age Group	Dose	Side Effects
Engerix-B (GlaxoSmithKline)	Hepatocellular Carcinoma	0 -19 yrs. 20 yrs. and older	0.5ml (3 doses) 1 ml (3 doses) 1st dose: At any given time 2nd dose: One month after 1st dose. 3rd dose: Six months after 1st dose	Soreness, swelling and redness at the injection site.
Sipuleucel-T (Provenge®)	Asymptomatic or minimally symptomatic metastatic castrate resistant prostate cancer.	≥ 65 yrs.	3 doses at approximately 2 weeks interval followed by leukapherisis	Chills,fever,pain, fatigue so patient is pretreated with Acetaminophen and Diphenhydramine.
GARDASIL™ (Human Papilloma Virus HPV Quadrivalent Types 6,11,16 & 18)	Cervical Cancer, Vulvar, Genital Cancer and Genital Warts.		3 DOSES Dose 1: At any given time. Dose 2: 2 months after 1st dose. Dose 3: 6 months after 2nd dose.	Pain, swelling, itch, bruising, Headache and fever.
Oncophage (Vitespen)	Kidney cancer, Metastatic melanoma, Glioma	Patients with early stage kidney cancer and	Four weekly doses and then biweekly doses.	Injection site reaction, fatigue, Headache.

		recurrent glioma as therapeutic vaccine		
Cervarix (HPV Bivalent 16,18)	Cervical cancer, Cervical Intraepithelial Neoplasia(CIN) Grade 1 & 2	9-25 yrs.	3 doses 0.5 ml Intramuscularly following schedule 0, 1 & 6 months.	Pain,redness,swelling, G.I. symptoms.
Recotumomab (Vaxira)	As therapeutic vaccine for recurrent and advanced Non - Small Cell Lung Cancer (NSCLC)		Recotumomab alum solution is administered intradermal every 14 days for the 1st 2 months followed by monthly booster dose.	Flu like symptoms, Mild to moderate injection site reaction(erythema, Induration, pain) which disappears in 24-48hrs.

Table 9: Selected Cancer Vaccines in Phase 3 Clinical Trials [18]

Company (location)	Product description	Indication
Antigenics (Lexington, Massachusetts)	HSPPC-96 Oncophage: heat-shock protein vaccine isolated from patient tumor cells	MelanomaGliomaRenal cell carcinoma
BioVest International (Tampa, Florida)	Biovaxid: patient-specific immunoglobulin idiotype vaccine conjugated to the immunogenic protein KLH	Non-Hodgkin's lymphoma
Genitope (Fremont, California)	Patient-specific immunoglobulin idiotype-KLH conjugate	Non-Hodgkin's lymphoma
GlaxoSmithKline (Brentford, UK)	MAGE: liposomally packaged tumor-specific antigen	MelanomaLung cancer
Northwest Biotherapeutics (Bethesda, Maryland)	DCVax: patient-derived dendritic cells loaded with cancer proteins or lysates	Prostate cancerBrain cancer
NovaRX (San Diego)	Lucanix: four cell lines carrying antisense oligos against transforming growth factor	Lung cancer
Oncothyreon (Seattle)	Stimuvax: liposomal vaccine with a synthetic peptide derived from tumor-specific antigen MUC-1	Lung cancer
Oxford Biomedica (Oxford, UK)	TroVax: pox viral vector carrying tumor-associated antigen 5T4	Renal cell carcinoma

CONCLUSION

According to various diverse vaccine platforms that have been evaluated, Cancer vaccines are considered as promising, emerging therapeutic options. The study emphasizes the goal of

vaccine-based cancer immunotherapy as effective and ultimate approach that elicits a potent immune response causing the eradication of the tumor as well as generates a long-term memory response thus guaranteeing complete remission. Presently available cancer vaccine approaches, including dendritic cell-based, tumor-associated antigen peptide-based, and whole cell-based, have various pros and cons, till date. Also, it should be noted that vaccines are need to be combined with immunoregulatory agents to overcome tumor-related immunosuppression. Thoughtful clinical trial design and abundance of concepts coming from laboratories suggests a thorough evaluation of cancer vaccines at an early stage and it's believed that by the next decade there shall be an unprecedented growth in the development of effective cancer vaccine.

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