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Review Article

Cancer Vaccine: An Overview

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Abstract: Cancer is an uncontrolled growth of cells that invade surrounding tissue replacing native cells resulting in disease and finally death. Mutation in genes that encode cell cycle proteins causes cancer. Development of cancer vaccine is the need of the century. 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. Success of cancer vaccine appears to be limited. Targeted vaccines become ineffective as the target mutates. Genetically engineered vaccines may prove to be ineffective as neutralizing antibodies may be produced. Adjuvants used for poorly immunogenic vaccines may prove to be toxic. Thus, the development of effective cancer vaccines require continued efforts, thoughtful clinical trials, and scientific progress which might induce long-term specific anticancer response with immune memory cells, and could contribute to effective and lasting elimination of malignant cells.
Keywords: Cancer, cancer vaccine, recombinant vaccines, adjuvants, clinical trial.

INTERODUCTION

Cancer is a fatal disease caused by environmental factors that mutate genes encoding critical cell-regulatory proteins. The resultant aberrant cell behaviour leads to expansive masses of abnormal cells that destroy surrounding normal tissue and spread to vital organs resulting in disseminated disease, commonly a harbinger of imminent patient death. [1]

In spite of significant progress in recent years towards the development of new targeted therapies, cancer remains a largely unmet medical need and the leading cause of death in industrialized countries [2].

Cancer prominence in the western world rose from the nineteenth century to become "a disease of civilization.''[3].Cancer death rate in America, after climbing unrelentingly for a century, peaked in 1990. Since then it has dropped by 12 percent back to its level in 1960. Cancer still claimed 564 thousand American lives in 2004, which constituted 24 percent of deaths from all causes [4].

The picture is a little different in the developing countries, where cancer death rate is lower but rising. Worldwide in 2000, cancer caused 6.7 million deaths. The World Health Organization estimated that if unchecked, annual global cancer deaths could rise to 15 million by 2020 [5]. Currently there are several techniques that are being used to treat cancer like Angiogenesis Blockers, Bone Marrow Transplants, Chemo Therapy, Cryosurgery, Gene Therapy, Laser Therapy, Photodynamic Therapy, Radio Therapy & Stem Cell Therapy [6].

Types of cancer

According to conventional allopathic medicine there are over 150 types of cancers that can be categorized as carcinomas, sarcomas, leukemias, lymphomas, and myelomas [7,8].

Scientists are developing several experimental cancer vaccines that could lead to the eradication of cancer this century.
The term *cancer vaccine* refers to a vaccine that prevents infections with cancer causing viruses, treats existing cancer or prevents the development of cancer in certain high risk individuals [9].

Vaccine development is one of the most promising and exciting fields in cancer research; numerous approaches are being studied to developed effective cancer vaccines. The aim of this form of therapy is to teach the immune system to recognize antigens that escaped the immunologic surveillance and are 'tolerated' by it, therefore able to survive and, in time, disseminate [10].

There are two broad types of cancer vaccines:

Preventive (or* prophylactic*) vaccines: which are intended to prevent cancer from developing in healthy people; and

Treatment (or* therapeutic*) vaccines: which are intended to treat an existing cancer by strengthening the body's natural defenses against the cancer [11].

There are two major categories that cancer vaccines fit into:

Specific Cancer Vaccines – Treat specific type of cancers. Different vaccines are needed to treat different types of cancers.
Universal Cancer Vaccines –Fight cancer cells regardless of cancer type [12].

DIFFERENT KINDS OF CANCER VACCINES

Antigen vaccines

Antigen vaccines use tumor specific antigens to stimulate the immune system. The antigens are usually proteins or peptides. By injecting these antigens into the cancerous area of the patient, the immune system produces an increased amount of antibodies or cytotoxic T lymphocytes/ killer T cells. Antigen vaccines boost the immune system by using only one antigen (or a few) [13]. Tumor immunotherapy can generally be classified as (a) passive (or adaptive), consisting of administration of cells or antibodies ex vivo, and (b) active, represented by vaccines, aimed at eliciting a specific immune response against tumor-specific antigens (TSAs) and tumor-associated antigens (TAAs). Both have their specificities as well as limitations [14, 15].

In cancer, most antigens are derived from mutated or modified self-proteins against which there is often a certain level of immune tolerance. To elicit anti-tumor immunity without autoimmunity the vaccines have to overcome this tolerance & design of such appropriate vaccine is a great challenge [16].

Tumor Cell Vaccines

Whole-cell tumor vaccines have been investigated for more than 20 years for their efficacy in both preclinical models and in clinical trials in humans. There are clear advantages of whole-cell/polyepitope vaccination over those types of immunotherapy that target specific epitopes. Multiple and unknown antigens may be targeted to both the innate and adaptive immune system, and this may be further augmented by genetic modification of the vaccine cells to provide cytokines and co-stimulation [17].

Whole tumor cells are a good source of TAAs and can induce simultaneous CTLs and CD4 (+) T helper cell activation. Current approaches prepare whole tumor cell vaccines, including traditional methods of freeze-thaw lysates, tumor cells treated with ultraviolet irradiation, and RNA electroporation, along with more recent methods to increase tumor cell immunogenicity with HOCl oxidation or infection with replication-incompetent herpes simplex virus [18].

Tumor cell vaccines may be:

- **Allogeneic:** vaccines made from melanoma tumor cells taken from individuals other than the patient.
- **Autologous:** vaccines made from melanoma antigens taken from a patient's own cancer cells

A variety of cancer cells and cell fragments are used in tumor cell vaccines:

- Whole tumor cells.
- Tumor lysates: fragments of destroyed tumor cells.
- Tumor oncolysates: an extract made from cancer cells infected with a strain of virus destructive to the cancer cells.
- Apoptotic bodies: fragments of cells that have died a natural death.
- Transduced tumor cells: cancer cells that have been altered through genetic engineering to include genetic material from cytokines, proteins that stimulate the activity of immune cells, including cytotoxic T cells **[19].**

A major disadvantage of whole-cell tumor vaccines is that tumor cells, as such, are generally not immunogenic. Other approaches such as the use of purified fractions of allogeneic tumor cell lines as antigens that are shed by the tumor cells into the culture media have been used to improve immunogenicity [20].

An adjuvant is an ingredient added to a vaccine to improve the immune response it produces. Currently, the only adjuvant licensed for human use in the United States is an “alum” adjuvant, which is composed of aluminum salts [21]. In addition to alum, oil-in-water emulsions & monophosphoryl lipid (MF59®) + alum, known as AS04 are the two other adjuvants used in approved vaccines [22].The design of cancer vaccine adjuvants has evolved with the understanding that the synergy of conserved pathogen associated molecular patterns (PAMPs) with specific pattern recognition receptors (PRRs) and downstream signalling leading to activation of NF-kB and IRF- 3 and expression of pro-inflammatory cytokines forms the basis of innate immunity [23]. Many cytokines that are produced in response to activation of innate immunity continue to be used individually as recombinant proteins, fusion partners with selected TAAs and co-expressed with TAAs in gene based cancer vaccines [24]. Perhaps the most significant development of cancer vaccine adjuvants has been the addition of various TLR (Toll like receptors) agonists to vaccine formulations, including TLR-3, TLR-4, TLR-5 TLR-7 TLR-7/8, and TLR-9 [25-27]. Either individually or in concert, these TLR agonists have been shown to significantly enhance vaccine potency. The TLR-targeted adjuvants are typically formulated as microparticles/ nanoparticles or liposomes, along with selected antigens [28].

Preclinical findings and clinical applications of TRICOM based vaccines as cancer immunotherapy

were reviewed. It was found that TRIad of COstimulatory Molecules (TRICOM; B7-1, ICAM-1 and LFA-3) enhanced T-cell responses to TAAs to levels far greater than any one or two of the costimulatory molecules in combination [29].

Anti-Idiotype antibody-based Vaccines

Immunoglobulin (Ig) molecules contain highly specific, unique peptide sequences in their variable regions at the antigen-combining sites in the complementary-determining regions. These form the unique antigen recognition site of the Ig protein and contain determinants that themselves can be recognized as antigens, or idiotypes [30].

The idiotype of each V region of a single immunoglobulin molecule may comprise of as many as 15–20 idiotopes, which can be distinguished by monoclonal anti-idiotypic antibodies or defined by a specific and unique amino acid sequence. Both the binding specificity and the idiotype of an antibody are determined mainly through recombination events that occur after exposure to a specific antigen. These idiotypes are more likely to be sequence- dependent, and linear antigenic determinants. The hypervariable regions (CDRs) are thought to be the primary immunogenic sites within the variable region, but any part of the variable region of immunoglobulin may contribute to the structure of an idiotype. In a number of systems, the CDR3 region has been shown to be the highest contributor; however, contributions by CDR1 and CDR2 are not uncommon [31].

Chemotherapy followed by idiotype vaccination with or without GM-CSF seems to be an effective regimen to immunize against lymphoma; several investigators are trying to improve this approach. One process under evaluation is the use of DCs pulsed with idiotype protein. Results of the first clinical trial in patients with relapse follicular lymphoma have been encouraging, with evidence of both cellular immune responses and clinical responses in approximately 30% of patients [32].

Dendritic Cell Vaccines

Dendritic cells (DCs) are considered the most potent APC of the immune system, and are unique in their ability to stimulate naïve T cells. DCs are adapted to capture proteins, proteolytically digest them, and present the resulting peptides on their cell membranes bound to MHC antigens [33].

Investigators are using tumor antigens alone or in combination with dendritic cells in various forms to constitute vaccines. Therapies are being delivered to many patients with different types of cancer in order to combat bulky disease, eliminate micro-metastatic disease, and provide a memory mechanism to fight tumor recurrence [34]. Several DC-based cancer vaccines have been developed to date including DC loaded with, tumor peptides or whole proteins [35],with tumor-derived mRNA or DNA [36], DC transduced with viral vectors such as retroviruses [37], lentiviruses [38] , adenoviruses [39], fowl pox [40] and alphaviruses [41] containing the tumor antigen or gene of interest, whole necrotic or apoptotic tumor cells [42], tumor cell lysates [43] and DC-fused with tumor cells [44, 45]. Although the potential of DC-based vaccines to induce an antigen-specific response have been shown in many clinical trials and preclinical animal models [46], choosing the best DC population from several DC cell subsets with distinct properties and functions has been a challenge. Each subset of DC has a unique capability of activating either Th1, Th2 or Th17 cells [47]. Once a particular DC subset has been isolated or generated, it must undergo a maturation process to enhance its ability to activate T cells. Recent studies have proved that as compared to immature DC, mature DC induce a superior immune response and correlate with a better clinical outcome [48-50].

Studies have also shown that co-administration of toll-like receptor 9 agonists, CpG oligodeoxynucleotides, can promote DC vaccines to break immune tolerance to tumor antigens. The therapeutic efficacy of in vivo DC activation has been investigated by directly administering glioma cell lysate with CpG oligodeoxynucleotides (CpG/lysate) in glioma-bearing mice. Results suggest direct vaccination with CpG/lysate provides an alternative and effective approach to induce host antitumor immunity and warrants clinical investigation in the immunotherapy of cancer [51].

It seems that an advantageous treatment option may be cellular immunotherapy with dendritic-cell vaccines which might induce long-term specific anticancer response with immune memory cells, which could contribute to effective and lasting elimination of malignant cells [52]. Many animal studies have demonstrated that the DCs/tumor fusion vaccine not only provided protection against challenge with tumor cells, but also regressed established tumors, including melanoma [53-56], colorectal [57-62], breast [63-64], esophageal [65], pancreatic [66], hepatocellular [67–70], lung [71], laryngeal [72], renal cell carcinoma [73], sarcoma [74], myeloma [75], mastocytoma [76], and neuroblastoma [77].

DNA Vaccines

DNA vaccines are bacterial plasmids constructed to express an encoded protein following in vivo administration and subsequent cell transfection. DNA vaccines have many advantages for tumor antigens. First, to some extent, encoded antigens can enter the processing and presentation pathways of the immune system and induce adaptive (antibodies, helper T cells, and cytotoxic lymphocyte) and innate immune responses in a manner similar to natural infection. Second, non-specific innate immunity stimulation,

which can act against tumor growth, is provided by the bacterial DNA backbone [78-82].

The reasons for the failure of DNA vaccines to induce potent immune responses in humans have not been elucidated. With further optimization DNA vaccine strategies can be improved, with significant effects on the outcome of immunization. Efforts to improve DNA vaccines have resulted in their enhanced efficacy in animals. However, the uptake of DNA plasmids by cells upon injection is very inefficient. Nowadays, two basic strategies have been applied for increasing DNA vaccine potency:

I. Physical approaches

1. Tattooing
2. Gene gun
3. Ultrasound
4. Electroporation
5. Laser

II. Viral and non-viral delivery systems

1. Biological gene delivery systems (viral vectors)
2. Non-biological gene delivery systems (non-viral vectors) such as:
   - 2.1. Cationic lipids/liposomes
   - 2.2. Polysaccharides and cationic polymers
   - 2.3. Micro-/Nano-particles
   - 2.4. Cationic peptides/Cell-penetrating peptides (CPP**)**

Both approaches are effective in animal models, but have yet to be evaluated fully in human clinical trials [83-85].

The only drawback of DNA vaccines, especially if using oncogenic DNA, is the potential of the DNA to integrate into the genome of the cell that takes it up, thus promoting malignancy. Using RNA instead, a more recent approach, can avoid the integration problem [86].

Viral-vector based vaccines

Vectors based on recombinant viruses have shown great promise and play an important role in the development of new vaccines. Many viruses have been investigated for their ability to express proteins from foreign pathogens and induce specific immunological responses against these antigens *in vivo*. Generally, gene-based vaccines can stimulate potent humoral and cellular immune responses and viral vectors might be an effective strategy for both the delivery of antigen-encoding genes and the facilitation and enhancement of antigen presentation [87]. Vectors are self-adjuvanted and offer the ability to express multiple TAAs along with an array of immune co-factors, arguably, they have yet to demonstrate convincing efficacy in pivotal clinical trials. However, in recent years, more coordinated studies have revealed mechanisms to optimize current vectors and have lead to the development of new advantageous vector systems. The major disadvantage of some vectors is that host-induced antibodies can neutralize the vector and limit its efficacy with repeated use [88, 89].

The first viral vector used was *Vaccinia*, a poxvirus, over 20 years ago [90]. Several other vectors have been developed based on the poxviruses, such as the modified *Vaccinia* virus Ankara (MVA) [91], and avian poxviruses, such as fowlpox [92] and canarypox [93-95]. Naked DNA and RNA can be made more immunogenic by incorporating them into viral vectors.

These vectors facilitate the production of high levels of proteins inside the cells that are transduced. Also, the vector itself can provide an adjuvant effect, enhancing the immune response against the transgenic protein. Although a single vector should not be seen as a universal vaccine carrier appropriate for use in vaccine development against every disease, the characteristics of each virus vector-based vaccine can be exploited for use in specific cases. Moreover, the feasibility of administering viral vector-derived vaccines in combination modalities with other vaccines gives these vaccines an additional advantage [92]. In vivo experiments have shown that mice immunized with the combined approach of Ad5-PSA and CpG had enhanced protection against the subsequent tumor challenge as compared to mice immunized with vaccine alone [96].

HPV-related cancers, low-grade neoplasia, genital warts, and RRP constitute a substantial public health burden. A prophylactic quadrivalent HPV 6/11/16/18 vaccine is highly effective in reducing the risk of HPV 6-, 11-, 16-, and 18-associated anogenital diseases. There are ongoing studies to evaluate vaccine efficacy in men and adult women. Immunization with this vaccine holds promise for reducing the overall burden of clinical HPV disease [97].

Limitations of Cancer Vaccines

Today, most cancer vaccines are targeted. The limitations of targeted vaccines are very similar to the limitations of other targeted therapies like mAbs; i.e. not all patients' antigens are the same and tumor cells and their antigens mutate. In other words, when the targets change, the targeted vaccine becomes ineffective. Moreover, cancer cells used for the development of vaccines contain a high proportion of targets which are not cancer cell-specific, and an enrichment of cell surface material is needed to improve the effectiveness of cancer vaccines. Response of "targeted therapies" appear to be around 20 to 30 percent [98, 99].

Autologous vaccine therapy being very costly may also cause auto-reactivity and the subsequent development of an autoimmune disease. Patients treated with genetically engineered vaccines may produce neutralizing antibodies, which could cause subsequent

therapies with the same product to become ineffective. The use of adjuvants in poorly immunogenic vaccines may increase immunogenicity of the vaccine, but may also cause increased toxicity [98].

While cancer vaccination itself is a promising novel approach, its combination with additional therapies could produce much more synergistic effects [100].

Table for cancer vaccine [101-103]

Company	Product	Description	Indication	Trial phase
Whole-cell-based autologous cells (personalized)				
Avax Technologies	M-Vax	Autologous cell vaccine in which patient tumor cells are treated with the hapten dinitrophenyl	Metastatic melanoma with at least one tumor to create vaccine	Phase 3
Dendreon	Provenge	Autologous dendritic cells exposed *ex vivo* to fusion protein combining prostate alkaline phosphatase and GM-CSF	Asymptomatic, metastatic hormone-refractory prostate cancer	Phase 3
Geron	GRNVAC1	Autologous dendritic cells transfected with mRNA for human telomerase and a portion of lysosome-associated membrane protein (enhances antigen presentation)	AML in remission	Phase 2
IDM Pharma	Bexidem	Autologous interferon- ϒ-activated macrophages	Superficial bladder cancer	Phase 2/3
	Uvidem	Autologous dendritic cell vaccine loaded *ex vivo* with tumor antigens derived from resected tumor	Melanoma with M1a or M1b stage disease and/or in-transit lesions; stage III and IV melanoma	Phase 2
	Collidem		Colorectal cancer	Phase ½
Introgen Therapeutic	INGN 225	Dendritic cells treated with an adenovector carrying the human p53 gene	Advanced metastatic SCLC Breast	Phase 2
MolMe	M3TK	T cells bioengineered to express MAGE 3 tumor antigen	Metastatic melanoma	Phase 2
Northwest Biotherapeutics	DC-Vax Prostate	Dendritic cells loaded with recombinant prostate-specific membrane antigen (PSMA)	Hormone-dependent, nonmetastatic prostate cancer	Phase 3
	DC-Vax Brain	Dendritic cells loaded with tumor extract	Newly diagnosed glioblastoma multiforma requiring surgery, radiation and chemotherapy	Phase 2
Prima Biomed	CVac	Dendritic cells primed with a	Late-stage ovarian	Phase 2

Company	Product	Description	Indication	Trial phase
		mucin-1 and a mannan-fusion protein adjuvant	cancer	
Whole-cell-based allogeneic tumor cells (off-the-shelf)				
Cell Genesys	GVAX pancreatic	Two allogeneic cultured cancer lines, irradiated and bioengineered to secrete GM-CSF.	Metastatic pancreatic cancer	Phase 2
	GVAX leukemia	One allogeneic leukemia cell line irradiated and bioengineered to secrete GM-CSF	Newly diagnosed AML, chronic CML and myelodysplastic syndrome	Phase 2
NovaRx	Lucanix	Four non-small cell lung cancer cell lines carrying antisense oligonucleotides against transforming growth factor β-2	Advanced NSCLC	Phase 3
Onyvax	Onyvax-P	Three human cell lines representing different stages of prostate cancer	Hormone-resistant prostate cancer	Phase 2
Unique-antigen-based (personalized): purified peptide or protein				
Antigenics	HSPPC-96 Oncophage	Heat shock protein vaccine purified from autologous tumor cells	Recurrent glioma	Phase 2
			Resected renal-cell carcinoma (RCC)	Phase 3
Biovest International	BiovaxID	Tumor-specific idiotype conjugated to keyhole limpet hemocyanin, plus GM-CSF	Mantle cell lymphomaIndolent follicular B-cell non-Hodgkin's lymphoma	Phase 2 Phase 3
Shared antigen (off-the-shelf): purified protein or peptide				
Apthera	NeuVax	Immunogenic peptide derived from the Her-2/neu protein plus GM-CSF	Early-stage Her-2-positive breast cancer	Phase 2/3
CellDex	CDX-110	A 14-amino-acid segment of a mutated EGFR	Glioblastoma multiforme	Phase 2/3
Cytos Biotechnology	CYT004-MelQbG10	Modified fragment of the Melan-A/MART-1 protein coupled to the carrier QbG10	Advanced-stage melanoma	Phase 2
Generex Biotechnology	IiKey/HER2/neu cancer vaccine	Peptide vaccine containing Ii-Key modified Her-2/neu protein fragment	Node-negative breast cancer	Phase 2
GlaxoSmithKline Biologicals	MAGE-A3 antigen-specific cancer immunotherapeutic	Liposomally packaged cancer vaccine against MAGE-3 antigen	Metastatic MAGE-A3-positive melanomaNSCLC following surgery	Phase 3 Phase 3
IDM Pharma	IDM-2101	Nine CTL epitopes from four tumor-associated antigens, including two proprietary native epitopes	NSCLC	Phase 2

Company	Product	Description	Indication	Trial phase
		and seven modified epitopes and one universal epitope (a source of T-cell help)		
Immatics Biotechnologies	IMA901IMA910	Peptide vaccine comprising multiple fully synthetic tumor-associated peptides	Renal cancerColorectal cancer	Phase 2 Phase ½
Norwood Immunology	Melanoma cancer vaccine	Melanoma-specific peptides gp100 and MAGE-3	Melanoma	Phase 2
Oncothyreon	Stimuvax	Liposomal vaccine containing a synthetic 25–amino-acid-peptide sequence from MUC-1	Stage lll NSCLC	Phase 3
Pharmexa	GV1001	Recombinant protein vaccine targeting human telomerase reverse transcriptase, plus GM-CSF	PancreaticLiverLung	Phase 3 Phase 2 Phase 2

CONCLUSION

The vaccine development for Cancer is an exemplary approach of researchers to fight the most dreadful disease around the globe. Many clinical trials are underway to test vaccines as potential treatments for a wide variety of cancer types. Research in molecular biology and immunology has resulted in the development of a range of recombinant vaccines. As of yet success with cancer vaccines is limited. Evidence is emerging that vaccines will work synergistically with established cancer therapies such as chemotherapy, surgery, immunotherapy, and radiation. Thus, there is a need for relevant preclinical and early clinical studies to further evaluate these approaches.

Future clinical trials will also need to incorporate more extensive monitoring of immune responses to help determine how vaccines induce effective tumor immunity, and to validate specific assays that correlate with clinical responses. Finally, almost all of the clinical trials of cancer vaccines have been in patients with advanced-stage disease. The ability of these vaccines to prolong survival in patients with early stage disease and low tumor burden needs to be further explored.

Many unanswered questions and challenges lie ahead. Optimization of strategies, route, timing, and dose of administration will be critical in the development of cancer vaccines. Continued efforts, clinical trials, and scientific progress will allow the development of more potent targeted therapies for cancer patients.

In summary, it is critical that strategies being developed for cancer vaccines be based on clearly defined cellular and molecular targets. We must design rational combinations that act upon several cellular types, including initiators of the immune response (APCs) and effector cells (T cells). Finally, thoughtful clinical trial design is imperative to evaluate cancer vaccines at this early stage. Given the abundance of concepts coming from the laboratories, the next decade presages unprecedented growth in the development of effective cancer vaccines**.**

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