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# Cancer Vaccine : A Review.

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ABSTRACT

The cancer vaccine refers to a vaccine that either prevents infections with cancer causing viruses / treats existing cancer or prevents the development of cancer in certain high risk individuals. Vaccine can induce antitumor immune response in humans with cancer. Understanding the molecular events in the oncogenic potential of virus and tumor specific immune response plays a key role in efficacy of vaccine. This article reviews the role of oncogenic virus in pathogenesis of malignant transformation, prophylactic and therauptic approach, various models of cancer vaccine, candidate vaccine for Human Papilloma Virus, Epstein Barr Virus and acceptance of cancer vaccine.



## INTRODUCTION :

A large number of agents cause genetic damage and induce neoplastic transformation of cells, these agents are termed as carcinogens. Carcinogens can be chemical, radiation/ ionization, microbiologic. In later case more commonly virus is involved in neoplastic transformations. It's association in oncogenesis, is termed viral oncogenesis. The DNA virus like Human papilloma virus, Epstein Barr Virus, Kaposi's sarcoma virus Hepatitis B virus and RNA virus like Human T Cell leukemia Virus, HIV are known to be involved in the neoplastic process. Pasteur in his investigations of rabies in dogs, suspected that diseases is caused due to "too small microbe", Beijernick coined the term "virus" , association of virus with neoplasia was first observed by an italian physcian Sanarelli in 1889[1]. (Myxomatosis of rabit with pox virus), Peyton Rous's has been credited with Nobel prize in 1968[1], for his original work pointed out when the cell free extracts injected, induce sarcoma in chickens with in weeks. Edward Jenner showed that vaccination against cowpox provided protection against smallpox, which was the most common cause of death among young children at the time[1]. Infectious agents make up one important class of environmental factors implicated in tumour development and prophylactic vaccine have a long history of success in preventing non malignant disease induced by infectious agents[2]. The term cancer vaccine refers to a vaccine that either prevents infections with cancer - causing viruses, treats existing cancer or prevents the development of cancer in certain high risk individuals. Vaccination against an infectious neoplastic agent can be categorized based on three clinical application: (1) As a prophylactic vaccine to prevent infection or acute disease, (2) As a therapeutic vaccine to treat an established infection before a malignancy has been induced, (3) therapeutic vaccine to treat the infection after the malignant tumor has developed[3]. Thus an ideal vaccine would be

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effective both in preventing and in treating infectious disease, as well in reducing likelihood of transmission of the agent to uninfected individuals. Some cancers such as cervical cancer, hepatocellular cancer vaccines against these such as HPV vaccine and Hepatitis B vaccine respectively will prevent those cancers.

## MICROBIOLOGIC CARCINOGEN AND ONCOGENETIC POTENTIAL :

Identification of infectious agent in etiology of malignant process helps in timely interference with the infection could prevent the tumor formation[4]. Reducing exposure to an identified carcinogen represents the principal approach. Critical information for vaccine development is the knowledge of which antigen can induce protective immunity. Strain difference or interaction between the infectious agent and environmental factors, host factors such as genetic polymorphism Eg: Human p53 is polymorphic at aminoacid 72, arginine / proline. Arginine containing p53 at position 72, more susceptible for degradation by E6[5]. The identified oncogenic infectious agents share at least four characteristics: (1) the ability to establish a chronic infection, (2) the actual establishment of chronic infection in those individuals destined to develop malignancy attributable to the infection, (3) an interval of many years between the initial infection and the development of malignancy, (4) a benign outcome for most infect individuals. Considering the current concepts of multistep carcinogenesis, the genetic alterations in targeted host cells, impairment of immune system probably involved in viral oncogenesis[5]. Infections induce the oncogenesis by three mechanism. (1) the agents such as HPV infects the potential target cell population and induce a series of changes from within those cells that lead to neoplastic alteration[6]. (2) the agents such as H. pylori infects the target tissue and induces cancer by local effects, usually chronic inflammation[7]. (3) it is more indirect, results in increased tumor risk secondary to suppression of the host immune system, as in case of HIV infection[8].

## PATHOGENESIS OF HPV AND EBV VIRUS :

### Human Papilloma Virus (HPV) :

HPV are known to be associated with cancer (Table 1). 70 genetically distinct types of HPV are identified[5]. HPV infects epithelial cells. Oncogenic potential of HPV can be related to E6 and E7 proteins.

Viral DNA is interrupted at constant site in the process of integration; it is always in the E1 / E2 ORF of viral genome. E2 region of viral DNA normally represses transcription of E6 & E7 early viral genes, its interruption causes over expression of the E6 & E7 proteins of HPV 16 & 18. E6 binds with p53 gene causing degradation of p53 through Ubiquitin proteolysis pathway, hence normal apoptosis is hampered and E7 binds with Rb gene causing the breakdown of complex RB - E2F complex causing deactivation of on /off of cell cycle, hence no cell cycle restriction[5]. (Fig.1)

**TABLE : 1**

| Lesion | HPV strains associated with lesion |
|---|---|
| Oral squamous papilloma | HPV 6,11. |
| Verruca Vulgaris (common wart) | HPV 1,2,4,5 and 57. |
| Condyloma Acuminatum | HPV 2,6,11,16,18,31,33,35. |
| Focal Epithelial Hyperplasia. | HPV 13, 32 |
| Carcinoma of Cervix | HPV 16 and 18. |

Lesions associated with HPV infection.

### Epstein Barr Virus (EBV) :

EBV infects epithelial cells of Oropharynx & B - Lymphocytes. The lesions associated with EBV are Burkit's lymphoma, Nasopharyngeal carcinoma, infectious mononucleosis, B cell lymphoma. EBV gains entry into B cells via CD21 molecule. In B lymphocytes, the linear genome of EBV circularizes to form an episome in cell nucleus. Infection of B cell is latent; no replication of virus / nor it is killed. Tumor suppressor gene is not targeted in EBV. EBV genes deregulate the normal proliferative & survival signals in latently infected cells[5]. EBV gains entry in to B cell via CD 21 receptor over the B cell. The EBV circularizes to form an episome, the Latent Membrane Protein (LMP) of EBV binds to CD 40 receptor of B cell. The activation of NFkB & JAK / STAT pathway promotes the B cell proliferation and Survival.(Fig 2)

The concomitant mutation like c -MYC translocation t(8;14) predisposes to Monoclonal proliferation of B cells progressing to Burkitt's lymphoma.(Fig 3).

## PROPHYLATIC VACCINE :

An ideal vaccine targeted to be effective both in preventive and in treating the premalignant disease also likelihood of transmission of the agent to uninfected persons. It is easier to carry out therapeutic clinical trials that determine efficacy than to conduct prophylactic

trials, since the response to vaccine can be evaluated with in a short span by suppression of infection and of the disease[3]. On contrary Plotkins suggested Despite advantage of vaccines with therapeutic efficacy, the challenge to develop such vaccines formidable. It has proven easier to develop prophylactic vaccines against infectious agents than therauptic ones. The vaccines that are approved are for prevention rather than treatment of infection[9]. As a normal theoretical and practical concern the vaccine stands important icon for prevention, since it makes the individual never affected by the agent. Hence in clinical trails of vaccine preparation the length of latent period between infection and malignant transformation remains important task. In case of infection, the cellular and humoral components of the immune system generally function together to interfere with infection or against the chronic infection. Antibodies capable of neutralizing the infectious agent appear to be prime effectors in preventing infection and CD 8+ T cells play a role in resolution of chronic infection[10]. The success of prophylactic vaccines in inducing long - term protection against infection probably lies in primarily in their ability to induce neutralizing antibodies[3]. Since the Papilloma virus contains Oncogenes, efforts to develop prophylactic vaccine have emphasized a subunit approach, analogous to HBV vaccine[11]. High level expression of L1 Major structural viral protein in non mammalin cells leads to its efficient self assembly in to Virus Like Particles (VLP's) resemble viral capsids structurally and antigenically. These VLPs are suitable immunogens, capable of raising high titres of neutralizing antibodies and are responsible for protection. The clinical trials in healthy human volunteers were injected intramuscularly with HPV 11, 16 L1 VLPs revealed inducing antibody titers and provided the protection[12]. there were no published records regarding interim analysis of the efficacy trial infection of other types of HPV other than HPV 16. Alternate approaches are being considered in HPV vaccination such as mucosal immunization with purified VLPs, use of non - pathogenic enteric bacteria that express L1 protein might be easier to deliver as prophylactic vaccine in developing world.

## THERAPEUTIC VACCINES :

Therapeutic vaccines are employed to treat an established infection before a malignancy has been induced and to treat the infection after the malignant tumor has developed[3]. The knowledge of molecular identities of tumor antigens and a well understanding of basic immunology will enable way to an effective the rapeutic cancer vaccine. The elicitation of tumor - specific immune response plays a pivotal role in an effective therauptic vaccine.

### Tumor Specific Host Immune Response :

The principle that T cells are important in the immune response against cancer, confirmed with studies in mice with methylcholanthrene - induced tumors[13]. T cells use structures on their surface called T cell receptors (TCRs) recognize peptide fragments of antigen called epitopes, these are noncovalently complexed with HLA molecules. Further studies on human and mice model by Overwijk WW et al suggested that CD8+ T Lymphocytes mediate tumor regression[14]. CD8+Tcells recognize MHC class I molecules presenting peptide epitopes. The epitopes are processed from intracellular proteins and then presented on the surface of the cells by MHC molecules. Antigen processing involves the cleaving of peptides from proteins with in the cell by proteasome, transporter protein is heteromeric dimer molecule called Transporter associated with antigen processing molecule. In endoplasmic reticulum, peptides make stable complexes with MHC class I molecules. After the completion of this cell journey, the MHC molecule along with antigenic peptide is potentially recognizable by a T cell. ( Fig 4) HLA molecules are polymorphic, HLA -A*0201 is expressed in approximately 40% of population[3].

Hence for effective therauptic vaccine lies in identification of tumor - associated antigen, suitable for therapeutic targeting. Early therauptic vaccine models is based on defined antigens, recombinant immunogens were created using the same virus. In animal models, these vaccines elicited powerful immune response that lead to tumor cell destruction, however failed in clinical trials[15]. A variety of techniques employed to identify tumor antigens recognizable by tumor - specific T cells, the more successful approach is transient transfection of pool genes from a tumor derived complementary DNA library[16]. Tumor antigens identified are poorly immunogenic in vivo, Tumor antigen in their original form bind poorly to their MHC molecules and T cell recognize their peptide - MHC complexes with low affinity. Thus enhancement of tumor antigen immunogenicity by modification of epitope sequences is necessary in processing

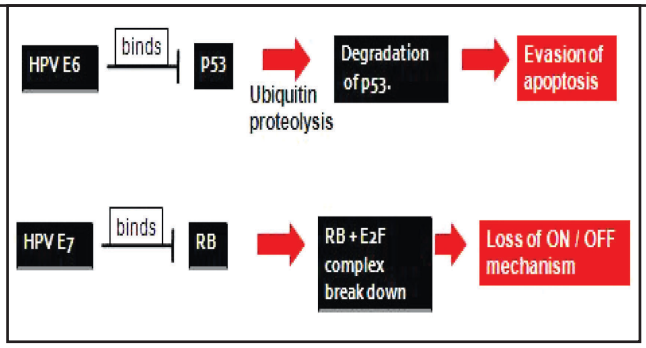


Fig 1:

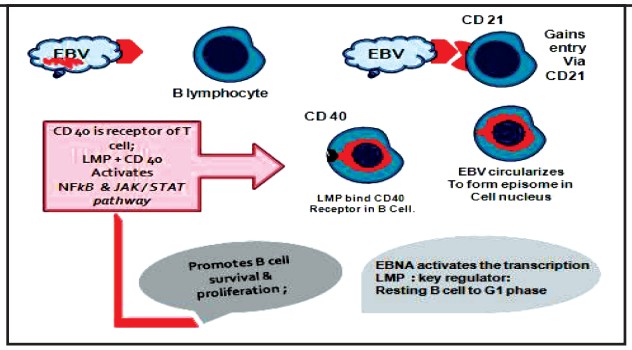


Fig. 2

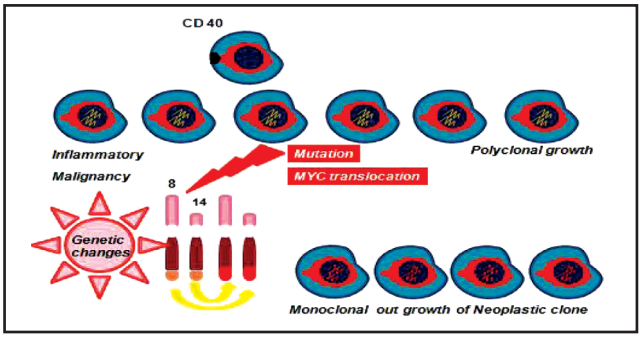


Fig. 3

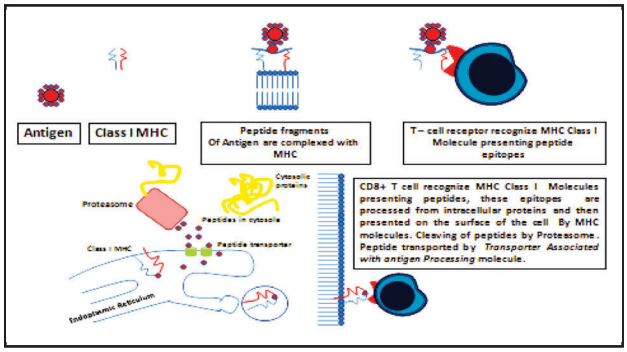


Fig. 4

**Fig 1:** Role of HPVE6 and E7 over tumor suppressor gene. **Fig 2:** Pathogenesis of EBV : gain entry in B lymphocyte.
**Fig 3:** Monoclonal proliferation of B cells : due to mutation of c- MYC translocation. **Fig 4:** Tumor specific Host immune response.

the therauptic vaccine. Hence altered peptides are capable of enhancing the stability of peptide - MHC complex due to modifications in the MHC anchor residues.17 Rosenberg et al suggested precursors of tumor specific T cells can be increased after immunization using different tumor associated antigens, including antigens that are non mutated ''self'' tissue differentiation antigens. The presence of increased antitumor T cell precursors after vaccination has been demonstrated using Enzyme - Linked Immunospot analysis (ELISPOT)[18].

## PROPHYLACTIC VACCINES VERSUS THERAPEUTIC VACCINES :

Prophylactic vaccines versus therapeutic vaccination cannot be used as an end point for the trials, because it is unethical to allow lesions to progress to malignancy, also end point would require more than 20 years long term study[19].

## CANCER VACCINE MODELS :

### Whole Cell and Lysed Cell Vaccines :

Whole cell autologous tumor vaccines contain relevant shared and mutated tumor antigens. Allogenic tumor cell vaccines, contains lysates of laboratory cell lines containing shared tumor antigens. Autologous is difficult to manufacture where as allogenic whole cell model are easier and practical to manufacture. Autologous and allogenic whole cell tumor vaccines stimulated limited immune response[20].

### Gene - Modified Tumor Vaccines:

Gene modified tumor vaccines contains of autologous tumor cells that have been transfected with an immunostimulatory gene. GM- CSF expressed in tumor cells are responsible for immune response and provides antitumor activity[21].

### Heat Shock Proteins:

Heat Shock Protein (HSP) activate CD8+ and CD4+ Lymphocytes, induce innate immune response that includes natural killer cell activation, cytokine secretion and induce maturation of dendritic cells[22].

### Peptide - Based Vaccines:

Peptides antigens that contain the appropriate HLA restricted aminoacid sequence, these peptides usually non immunogenic. Many immunodominant epitopes have a low binding affinity for MHC molecule, the low

binding affinity is due to lack of optical amino acids at the peptide anchoring sites. Peptide based vaccines demonstrates tumor derived peptides engineered to have an enhanced ability to bind to MHC molecules by substitution of amino acids at anchor positions.[23]

### Naked DNA :

Naked DNA vaccine, DNA plasmid immunogens contains antigen gene regulated by a promoter with constitutive activity that is conjugated with gold particles and injected in to skin using helium gas gene gun. The protein antigen produced by the target cells is taken by host Antigen Presenting Cells (APC) is processed, and cross - presented to the immune system in the draining lymph nodes[24].

### Viral Vectors :

A variety of viral vectors are employed in cancer immunotherapy. Tumor antigen DNA sequences inserted in to attenuated viruses that are unable to replicate in mammalian hosts. Ribas et al suggested recombinant replication - incompetent viral vectors which are modified viruses that have been specifically mutated to be incapable of self replication[25]. Enhancing the immune potency of recombinant viral vectors achieved by coexpression of cytokines or costimulatory molecules in viral vector. It includes Intracellular adhesion molecule -1 (ICAM 1), Lymphocyte Function associated Antigen 3 (LFA 3), and CD70. Pox virus have a large capacity to carry and express multiple genes[3].

### Ex Vivo Dendritic Cell Vaccines :

Dendritic cells (DCs) are potent antigen-presenting cells and play a central role in the initiation and regulation of primary immune responses. The fusion of DCs with whole tumor cells represents in many ways an ideal approach to deliver, process. Various antigen loading procedures used for dendritic cell antigen presentation. It includes using tumor lysates, messenger RNA (mRNA), apoptotic bodies fed to dendritic cells and these are taken up by endocytosis. T cells stimulated by DC/ tumor fusion cells are effective in lysis of tumor cells[26].

### Candidate Vaccines For HPV And Epstein Barr Virus :

### Human Papilloma Virus :

Manufacturers of HPV vaccines are Merck ( gardasil) and Glaxo smithkline ( cervavix ) it is adminsitred quadrivalent and bivalent respectively. Cuts et al categorized the characterstics of two candidate HPV vaccines, Merck group constitutes with VLP of genotypes 6,11,16,18, with substrate of yeast and adjuvant used are proprietary aluminium hydroxyphosphate sulfate, the schedule used in trials 3 intramuscular doses - two months between doses 1 and 2; six months between doses 1 and 3. It is safety in females and males aged between 9-15 yrs has been evaluated. Where as Glaxo smithkline (cervavix) constitutes with VLP of genotypes 16 and 18, substrate used was baculovirus expression system and adjuvants employed are proprietary aluminium hydroide and deacylated monophosphoryl lipid A. Schedule used in trials 3 intramuscular doses of 0.5ml with intervals of one month between doses 1 and 2; six months between doses 1 and 3. Its safety age group of females 10-14 and males of 10-18 yrs was evaluated[27].

### Epstein Barr Virus Vaccine :

The vaccines of Epstein Barr virus focused towards minimizing the clinical consequences of primary infection rather than malignancies associated with virus attenuated EBV model for vaccination cannot be employed due to potential oncogenicity of virus which would not meet the licensing requirement.adoption of two separate approaches based on subunit vaccines. (1) Major envelope glycoprotein of the virus, gp340. It includes the major neutralising determinants of the virus.(2) another approach based on the induction of cytotoxic T cells specific to Epstein-Barr virus. This relies on reducing the clinical symptoms of infectious mononucleosis rather than preventing primary infection. This established the important principle that specific cytotoxic T cells are capable of recognizing these Epstein-Barr virus-infected B cell[28] .

### Acceptance of Cancer Vaccine :

In general acceptance of vaccine is positive. Issues that to be explored is familiarity with cancer vaccine models, varied beliefs about risk of acquiring infections and concerns regarding the age specification for the vaccine. Elyse et al suggested that in case of HPV vaccine Parent and provider education should emphasize that adolescents are at risk for HPV infection and that to be most effective the HPV vaccine should be given to children before their sexual debut[29]. Vaccine education should target parental beliefs about HPV and the optimal age for HPV vaccine administration.

## CONCLUSION :

Vaccine models stands good example for "Prevention is better than cure". Cancer vaccine holds a glove in reducing exposure risk with a known agent. It's advancement and appropriation will be a prime position in decreasing cancer incidence globally. We have a sufficient literature and experimental trials that suggest cancer vaccines can induce antitumor responses. The success of candidate vaccine holds in understanding the molecular and cellular immunological aspects of agent and host response. Advancement in both prophylactic and therauptic vaccine, cost effectiveness, awareness helps in reducing morbidity and mortality rate.

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