Review Article

Current Strategies for the Development of a Therapeutic Cancer Vaccine – A Review

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ABSTRACT

The lack of effective cancer immunotherapies over the last few decades has led to the development of novel strategies in the field of therapeutic cancer vaccines. Hence, it could be argued that therapeutic cancer vaccines are on the verge of becoming primary immunotherapy for cancer. Such vaccines have undergone many transformations in the last decade. However, little is known about the biological and technological aspects of cancer vaccines. Improved understanding of tumor-specific antigens and novel delivery systems facilitate improved cancer vaccine design. The main goals of a cancer vaccine should be tumor deterioration, eradication of residual tumors, long duration of antitumor memory, and avoidance of adverse effects. These goals could be attained by improving biology and platform-based strategies for cancer vaccines. This review summarizes various biology and platform-based strategies from preclinical and clinical studies of therapeutic cancer vaccines.

Keywords: *Cancer, Cancer Immunotherapy, Cancer vaccines, Immunotherapy*

The principal aim of cancer immunotherapy including cancer vaccines is to activate the immunity targeted toward tumor cells while conserving the normal tissues. Tumors possess antigens which possibly will be recognized by the immune system. Spontaneous or vaccine-induced humoral and cellular immune responses precise to tumor antigens were distinguished in cancer patients. MAGE-1 is the first tumor antigen recognized by the T cells [1]. Subsequently, many tumor antigens were discovered. Tumor antigens are classified as tumor-associated antigens (TAA) and tumor-specific antigens (TSA) [2].

Cancer immunotherapies including cancer vaccines are the most promising approaches in oncology [3]. Prophylactic and therapeutic vaccines could be the most promising strategy for cancer treatment. In comparison to other cancer treatment modalities such as surgery, chemotherapy, radiotherapy, and adaptive immunotherapy; cancer vaccine-based therapy could be the most promising therapy owing to its capability to produce long-lasting immune responses against tumor antigens. Cancer vaccines could produce immune responses that could cure tumors or delay the recurrence of tumors and improve the overall survival of cancer patients. However, in most clinical trials results did not meet the clinical endpoint. Only, Sipuleucel-T (Provenge) was approved by the Food and Drug Administration in 2010 [4].

Access this article online	
Received – 08 May 2024 Initial Review – 07 June 2024 Accepted – 21 June 2024	Quick Response code
DOI: ***	

Moreover, the design and development of efficient cancer vaccines are halted due to hurdles such as deficiency of TSAs and delicate immune responses targeted towards TAAs [5]. Recently, numerous strategies were evaluated for improved cancer vaccine development. Different strategies used for the cancer vaccine include cell-based, gene-based, peptide-based, and viral/bacterial vector-based [6]. The shared agenda for all these strategies is to stimulate antigen-presenting cells and stimulation of antigen-specific cytotoxic T lymphocyte-mediated immune response. In most of the clinical trials cell, peptide, and virus-based strategies were implemented for cancer vaccine design owing to the existing information about safety, immune potential, and manufacturing [7].

Till 2016, more than 550 clinical trials were conducted for cancer vaccines. However, ≤5 trials were conducted for gene-based cancer vaccines. Among 550 clinical trials, most trials failed to demonstrate clinical endpoint in phase III trials. Despite this slow progression in cancer vaccine development, this entire field never came to a halt. In most of the trials, acceptable levels of toxicity and immunogenicity were the positive takeaways. Hence, scientists are putting all efforts into improving the efficacy of these vaccines [6]. At present, continuous efforts are being made to optimize the cancer vaccine design and development which can meet expectations.

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The objective this review is to add the comprehensive literature about recent developments in cancer vaccination. The collection of potential vaccination methodologies and challenges faced by the scientific community to cope with the global lung cancer spread is specially focused on in this review.

BIOLOGICAL STRATEGIES FOR CANCER VACCINE

1. DNA vaccine

DNA vaccines contain concentrated forms of tumor antigens. These vaccines are easy to manufacture with the advantage of built-in adjuvant benefits. However, DNA vaccines require additional steps such as transcription and translation before presentation by the antigen-presenting cells such as dendritic cells (DCs). DNA vaccines are more beneficial in producing $CD4^+$ T cell and $CD8^+$ T responses after administration through intramuscular route through electroporation [8, 9].

DNA-dependent vaccines proved beneficial in stimulating the immune system against weak tumor-associated antigens. Several strategies including Gene Gun and cationic liposomes were developed for DNA-based vaccines [10,11]. Moreover, multiple administration of cytokines such as GM-CSF and IL-2 is possible with DNA-based vaccines [12]. It was demonstrated that plasmid-encoded antigens are beneficial for improvement in the immune potential of DNA-based vaccines. DNA-based vaccines against tumor-associated antigens such as PSA, PAP, gp100, CEA, and hsp65 were proven effective in prostate cancer, melanoma, colorectal cancer, and head and neck carcinomas [13,14].

A DNA vaccine that acts against antigens such as HPV-16/HPV-18 E6 and E7 demonstrated beneficial effects in patients with cervical intraepithelial neoplasia. In a mouse tumor model, a DNA multi-neoantigen vaccine demonstrated a principal $CD8^+$ T response. Neoepitope-specific vaccines were being prepared through DNA encoding using chemokine genetic information which augmented dendritic cells (DCs) targeting to improve T cell and antibody responses [8,9].

2. RNA vaccines

RNA vaccine shares similarities with DNA vaccine in terms of straightforward manufacturing and build-in adjuvants. On the contrary to DNA vaccines, RNA vaccines do not require transcription [15]. Hence, RNA vaccines are nearer to the expression, processing, and presentation of MHC complexes. RNA vaccines are usually administered through direct injection in the lymph nodes and an intravenous route using lipoplex nanoparticle injection [16].

In melanoma patients, it was evident that administration of an mRNA vaccine comprising ten personalized neoantigens demonstrated vaccine-specific immune response and reduction in the incidence of metastatic episodes [17]. Intravenous injection of RNA lipoplex vaccine comprising of four antigens such as NY-ESO-1, MAGE-A3, tyrosinase, and transmembrane phosphatase with tensin homology demonstrated robust T cell response [18].

Moreover, augmented antitumor response was evident in murine tumor models through incorporating RNA of a RIG-I immunostimulatory with CTLA-4 antibody. Also, RNA vaccine proved beneficial in expanding chimeric antigen receptor specific T cells claudin 6 on specific solid tumors [19,20]. It indicates RNA vaccines can improve immunological tolerance towards tumor antigens. However, it should be proven in clinical trials.

3. SLP vaccines

Historically, peptide-based vaccines comprise MHC-1 binding short peptides which demonstrate robust T cell response. However, these vaccines demonstrate suboptimal response upon use along with mineral oil adjuvant. In comparison to the short peptides, SLPs demonstrated promising results in both premalignant and malignant patients when used in IFA [21].

In contrast to the short peptides, SLPs do not bind directly to the MHC I class molecules. However, SLPs require antigen processing and demonstration to the cytotoxic T lymphocytes with optimal immune-stimulatory co-receptors [6]. Short peptides demonstrate antigen presentation throughout the body while SLP vaccines demonstrate DC-targeted antigen presentation merely in the vaccine-draining lymph node [22,23].

Approximately 30 amino acids long SLPs can similarly accomplish processing steps as that of DCs [24]. Hence, SLPs can achieve optimal antigen presentation on MHC-1 molecules. It was demonstrated that the SLP vaccine targeted against NY-ESO-1 incorporated in the IFA emulsions in combination with poly-ICLC or CpG produced strong $CD4^+$ T cell and $CD8^+$ T cell response [25,26].

Likewise, RNA vaccines and SLP vaccines also demonstrated strong $CD4^+$ T cell and $CD8^+$ T cell responses for mutation-based neoantigens and shared tumor-associated antigens [24]. Moreover, SLP vaccination demonstrated effectiveness as monotherapy against oncogenic proteins E6 and E7 in patients with premalignant HPV-16-induced lesions [25]. In a preclinical model of melanoma, it was demonstrated that SLPs can target multiple epitopes. It can be exemplified using TAS0314, a peptide composed of four TAAs from Squamous Cell Carcinoma Antigen Recognized By T-Cells (SART)2 and SART3.

SLPSs targeted towards NeoAg demonstrated usefulness in the individualized patients. NeoVax which comprised 20 diverse SLPs with immunostimulatory adjuvants such as poly-ICLC demonstrated effect as a TLR-3 agonist [27]. It demonstrated Th1-skewed response in advanced melanoma and glioblastoma patients. It indicates that SLPs produce both polyfunctional and specific functions. In melanoma patients, NeoVax produced tumor regression post-ICB treatment [28].

4. DC based vaccine

DCs activated with adjuvant and loaded with antigens are termed as DC vaccines which were tested in several trials. DC vaccines are usually injected through the subcutaneous and intravenous route of administration. Antigens for the DC vaccines were usually pulsed with peptides respective to the TAA or neoantigens, mRNA electroporation, lentiviral transduction, myeloid-derived antigen-presenting cells reactive against tumors-DCs, fusion with tumor cells, and incubation with whole tumor lysate [29-31]. Melanoma neoantigen-specific T cells, specifically $CD8^+$ T cells, could be primed using peptide-pulsed DCs. In murine models, it was evident that exogenously administered DCs act as antigen donors in addition to the endogenous antigen-presenting DCs.

In most of the clinical trials, ex vivo differentiated monocyte-derived DCs were used for vaccination. However, differentiated monocyte-derived DCs did not demonstrate characteristics of co-stimulatory molecules and antigen processing and cross-presentation mechanisms [32]. It has been demonstrated that antibody-based vaccination targeted precise DC receptors. These vaccines tolerate improved augmented antigen load to the presenting DC which improves the efficacy of tumor vaccines. This strategy is based on the association of protein with tumor antigens. It facilitates targeting immunogen to DC in situ [33]. It was shown that targeting DC in *in vivo* studies through the B subunit of Shiga toxin (STxB), which attaches to Gb3 expressed by DC, resulted in the augmented expression of antigen-specific $CD8^+$T cells [34,35]. Based on the strategy of expression of molecules on DC modules, various vaccines were developed for example DEC-205, Clec9a/DNGR, XCR1, and CD11b [36,37]. In human studies also augmented cross-presentation was reported through antibodies against DC receptors named DEC-205 and Clec9a which resulted in substantial improvement in $CD8^+$T cell induction [38,39].

5. Gene-based cancer vaccine

Targeting tumor-associated antigens (TAA) and Neoantigens (NeoAgs) proved an effective strategy as a cancer vaccine [17,40]. A combination of TAA and anti-PD-1 proved beneficial in producing Th1-skewed polyclonal T-cell responses in Immune checkpoint blockade (ICB) patients [18]. RNA should be expressed in higher percentages in the undeveloped dendritic cells and the lipid-based delivery system prompted type 1 interferon response through TLR-7 facilitating T-cell expansion [41].

A combination of 2 TAAs and 10 NeoAgs produced T-cell responses with lessening of growing metastatic cancer. Evidence of synergy was evident among TAAs and NeoAgs with ICB through T-cell responses which were evident in both CD4 and CD8 compartments [17]. It indicates the potential of gene-based vaccines in combination with conventional immunotherapies in patients with high-density tumors.

6. Viral vector cancer vaccines

The synergy of ICB with NeoAg-based cancer vaccine derived from gorilla adenovirus demonstrated usefulness in the abolition of cancer [42,43]. Precisely, preclinical models demonstrated that viral vectors for cancer vaccines can be loaded with different antigens such as Mucin-1/brachyury (prostate-specific antigen) and IL-12 in glioma [44,45]. Clinical trials demonstrated that two NHP Ad vectors proved beneficial in the transfer of NeoAg cancer vaccines such as chimpanzee (ChAd68) and GAd20. Results from these trials demonstrated that CD8 T cell responses were evident for NeoAg after vaccination with ChAd68. High microsatellite unstable tumors were targeted through two vectors such as Gad20 and MVA for NeoAg-based vaccines [46]. The Nous-209 vaccine demonstrated synergistic action through four viral vectors for NeoAg peptides in patients with MSI-H tumors. Adenovirus-based vaccines demonstrated usefulness in the central nervous system. Delta-24-RGD in patients with high-grade glioma demonstrated a 20% improvement in the high-grade glioma patients [47].

7. Vaccine with Tumor Cells or Tumor-Cell Lysates

Many tumor cells or tumor-cell lysate vaccines were studied in preclinical and clinical models. OncoVAX is a composition of autologous tumor cells either with BCG as adjuvant or not. OncoVAX proved effective in reducing disease progression (41 %) in stage II; however, it did not demonstrate improvement in stage III patients. The overall survival rate was higher in stage II cancer patients after treatment with OncoVAX in comparison to the control group [48]. LipoNova is founded on the lysate of autologous tumor cells targeted for renal cell carcinoma. It was designed through a process in which lysate cells were preincubated with IFN- to sensitize antigenicity and tocopherol acetate was used to protect the cells throughout the incubation duration. LipoNova in renal cell carcinoma patients demonstrated overall survival improvement in comparison to the control group [1].

GVAX is designed for prostate cancer composed of cancer cell lines such as LNCaP and PC-3 which is improved through Aden-associated viral vector encoded with GM-CSF gene. Animal studies demonstrated that subcutaneous injection of prostate cancer cells produces an immune response marked by the intrusion of neutrophils, $CD4^+$ T cells, and apoptotic cells. Antigenic response through TSAs and TAAs was produced through the secretion of GM-CSF. GVAX demonstrated reassuring immunological and preclinical data; however, it could not meet the clinical endpoints in phase III clinical trials. However, the overall survival rate was improved after administration of GVAX [49].

8. Neoantigens

In the recent past focus has been shifted towards neoantigens [24,50]. Neoantigens usually refer to the mutated tumor antigens. Hence, the effectiveness of neoantigens is based on

the number of mutations per megabase in the tumor tissue which is termed as tumor mutational burden. High numbers of tumor mutational burden usually develop higher immune checkpoint inhibition (ICI) [51,52]. Usually, the host does not develop resistance to these neoantigens. Hence, these neoantigens develop strong immune responses to T cells both spontaneously and T cell-based responses. Neoantigens usually ascend in the tumors through different processes including somatic mutations and post-translational mechanisms which include glycosylation, phosphorylation, and citrullination [53,54]. It should be noted that a specific subset of neoantigens demonstrates T cell response [55].

Hence, precise selection of neoantigens is essential for improved clinical outcomes. Recently, many clinical trials demonstrated that neoantigens proved their immunogenicity through CD4+ T cell and CD8+ T cell antigen-specific immune responses. It proved beneficial in improving patient survival. A single-arm study in patients with melanoma reported that antigen spreading occurs due to T cell-specific immune response after administration of neoantigen-specific immune response (monocyte-derived DCs incorporated in neoantigens) [17]. T cell response development was demonstrated through the delivery of neoantigens in the draining lymph node using mRNA lipoplexes vaccine. Further, T cell response was analyzed and reported that 60 % was CD4+ T cell response and 25 % was CD8+ T cell response [27]. It indicates CD4+ T cell responses are preferred over CD8+ T cell responses [56].

9. Bacteria Based Immunotherapy

Bacteria-based immunotherapy plays a substantial role in eradicating tumors due to their intrinsic immune-stimulating characteristics in the tumor environment. They are essential in generating the anti-tumor immune response by initiating the antitumor response of specific and non-specific immune cells. According to the latest clinical studies, Actinobacteria of Firmicutes and Ruminococcus/Lachnospiraceae have been reported to provoke a strong anti-tumor immune response against melanoma patients [57]. Moreover, personalized bacteria have been engineered and developed to create an enhanced immune response against tumors [58]. The recent clinical evidence on Listeria-based tumor vaccines has validated the effective activation of the immune response against the tumor and the successful elimination of tumor cells [59].

With the advancement in bacteria-based cancer therapy, oral cancer vaccines made of bacteria are more explored. An oral vaccine made of Salmonella Typhi strain CVD915 was used in a pre-clinical study of breast cancer-bearing mice to evaluate its effectiveness against tumors and liver metastasis. The optimistic outcome of such a pre-clinical trial supported the development of VXM01, the first oral cancer vaccine. The anti-tumor effects of VXM01 were evaluated and validated on prostate cancer patients [60]. The conventional bacteria-based immunotherapeutic approach has been recently improved by multidisciplinary novel interventions which is proved by numerous pre-clinical and clinical studies and bacteria have shown promising anti-tumor effects in stand-alone and combination cancer therapies [61].

PLATFORM RELATED STRATEGIES

1. Novel delivery vehicles

In the recent past, technological advancements demonstrated a major impact on the gene and virus-based cancer vaccine platforms. Improvements in vaccine platforms were evident in the form of structure optimization, innovative cancer vaccine delivery systems, and superior epitope prediction tools. mRNA construction has been optimized and validated through improvements in the cell culture and viral vector production [62]. Also, mRNA-dependent platforms allowed faster sequence adoptions to adapt to the emergent resistance mutations [63]. Gene-based platforms were advanced through the omission of exogenous and immunogenic cargos. Moreover, it facilitates the administration of multiple booster doses [63]. RNA structures are optimized in such a way as to minimize damaging immune activation, improving safety, biodistribution, and immune contour [64]. Improvements in the platform-based technologies proved beneficial in the utility of mRNA sequences for targeting tumor antigens as well as immunomodulators, monoclonal antibodies, small interfering RNA, CART constructs, and their combinations [65]. mRNA-2752 proved beneficial in multiple malignancies, releasing pro-inflammatory cytokines and shrinking tumors [66].

Versatile viral vectors were introduced such as adenoviruses (non-human primate, NHP), parvoviruses (adeno-associated viruses), and poxviruses [Modified Vaccinia Ankara (MVA)] [67]. These viral vector-based strategies proved useful in transferring genetic information and inducing potent T-cell responses [68]. Newer strategies were developed to minimize pre-existing immunity through the introduction of prime or booster dose approaches dependent on two non-cross-reacting immunologically diverse vaccines [69]. Oncolytic viruses were used for *in situ* vaccination which proved beneficial in promoting immune responses against diverse epitopes owing to their inherent capability to replicate within the cancer cells [70]. Talimogene Laherparepvec received regulatory approval as an oncolytic virus. In pediatric high-grade gliomas, herpes simplex virus 1 G207 produces T-cell responses and tumor immune infiltration [71]. In the preclinical model, the immune response was boosted through genetically modified Maraba Virus post-ad-based vaccination [6].

Novel strategies were developed for the RNA-based platforms such as protamine combined, lipoplex, and lipid nanoparticles. It has been demonstrated that BNT162b2 and mRNA-1273 LNP as vectors for spike protein-encoding

mRNAs produced noteworthy safety profiles in sub-groups including cancer patients. It should be noted that the persistent level of antibody was evident for 6 months after the second booster dose [72,73].

2. Augmenting tumor specificity of cancer vaccine

The effectiveness of antigen-based therapeutic vaccines depends largely on the characteristics of the antigen present in the vaccine. Technological improvements proved beneficial in improving the selection of specific antigens. In most of the cases, shared tumor antigens were the focus as vaccine targets [74,75]. These shared antigens comprise self-antigens including over-expressed antigens, cancer testis antigens, and differentiation antigens; also, non-self-antigens including E6 and E7 proteins of human papillomavirus (HPV).

3. Shared antigen vaccine

Shared antigen vaccines are more beneficial for vaccine candidates with tumor mutational burden. Moreover, newer vaccine development platforms and innovative combination therapies provided more feasibility in the development of shared antigen vaccines [76]. A combination of four shared tumor antigens and anti-PDL-1 therapy in mRNA vaccines promote more induction of type I IFN which promotes T-cell recruitment [18]. Shared tumor antigens demonstrate high immunogenicity and more than 75% of patients respond to these vaccines with high immunogenicity.

Examples are also available where neoantigens are combined with shared antigen vaccines. APVAC1 and APVAC2 vaccines for the treatment of glioblastoma contain shared tumor antigens and patient-specific neoantigens, respectively. From the clinical study, differential response was evident for APVAC1 (CD8+ T cell response) and APVAC2 (CD4+ T cell response). In other examples of breast cancer treatment, the mRNA vaccine contains shared antigens and individualized neoantigens of the IVAC WAREHOUSE concept and IVAC MUTANOME concept respectively. Moreover, a full range of tumor antigens was developed using different strategies such as CpG-activated tumor cells, DCs fused with tumor cells, and DCs loaded with whole-tumor lysates [77,78].

a. Direct Administration of Antigen

Direct administration of antigens is the strategy where the concentrated form of antigen, 'which injected through varied routes such as intravenous, intramuscular, subcutaneous and intracutaneous', present the antigens to the DCs and its antigen processing pathways in a vaccine draining lymph nodes. Direct administration of antigens could be achieved through direct tumor antigen delivery using DNA, RNA, and synthetic long peptides (SLPs) [15,79]. All these direct antigen administration strategies demonstrated benefits in producing robust T-cell responses and therapeutic benefits against cancer.

b. Strategy for Indulgence Cross Presentation

Protein-dependent vaccines upon internalization in the cell, degrade in the peptides which are related to the Human leukocyte antigen (HLA) class II molecules. This complex is specifically presented to CD4+ T cells; however, it does not present to the CD8+ T cells. Cross-presentation is the process in which a few subpopulations of DC could activate MHC class I pathway extracellular proteins. Pathogen-derived delivery systems (virus and bacteria as vehicles) possess inherent characteristics to reach the cytosol. It favors MHC class I peptide presentation to produce specific CD8+ T cell response which is not evident in the free proteins and peptides. Moreover, pathogen-derived delivery systems are capable of producing natural immunogenicity through the expression of PAMP, activating molecules, and immunomodulatory molecules [80,81]. However, it can be argued that attenuated pathogen vectors should be used instead of live pathogen vectors to avoid the risk of bacteria and virus neutralization owing to host immunity. Other vehicles in the form of emulsion, liposomes, virosomes, and nanoparticles are available with the capability to promote cross-presentation to CD8+ T cells. However, murine data is available to demonstrate the effectiveness of these vehicles with the scarcity of human data [82, 83]. It should be noted that cross-presentation is precise to the DC sub-populations specifically to the CD141+ DC termed as cDC [84].

c. Non-antigen-specific ISVs

In situ vaccines (ISVs) are antigen-agonist agents that can improve endogenous anti-tumor response. ISVs exhibit their action through different mechanisms such as *in situ* activation of immune cells through stimulation of innate immune pattern recognition receptors (PRRs), activation of APCs receptors, introduction of ICD, antigen presentation augmentation, allowing T cell priming and memory T cell activation [85,86]. Most importantly, ISVs can target tumors at local and distal sites. Usually, ISVs act as activating agents for TLRs (PPRs) and stimulators of interferon genes protein (STING) [87,88].

Bacillus Calmette – Guerin (BCG) vaccine which is beneficial in non-muscle invasive bladder cancer exhibits its action through activation of TLR-2 and TLR-4 [89]. Imiquimod, beneficial in superficial basal cell carcinoma and transit melanomas, exhibits TLR-7 and TLR-8 agonist activity [90]. Other examples of ISVs include fms-like tyrosine kinase 3 ligand (FLT3L), CD40 receptor agonists, and CD40 activators [91,92]. However, it could be argued that alone FLT3L could not demonstrate effectiveness. FLT3L could demonstrate effectiveness in combination with other platforms [93,94].

Oncolytic viruses could produce ISVs which could produce an immune response locally and distally. These can be altered genetically or chemically to augment the expression of cytokines, antibodies, and co-stimulatory factors [95]. ICD

induction through oncolytic viruses facilitates the release of tumor-specific antigens consisting of neoantigens and enables neoantigen-specific T cells [96]. Oncolytic virus therapy, 'Talimogene Laherparepvec', is FDA-approved therapy. Moreover, it is being evaluated for combination therapy [97].

Other examples of oncolytic virus therapy include coxsackie virus, Newcastle disease virus, adenovirus, poliovirus type 1, reovirus, vaccinia, measles viruses, and flu viruses. Intratumor administration of immune-activating cytokines including GM-CSF, IL-12, IL-15, and IL-2 proved effective in producing antitumor T-cell and NK cell responses [98]. ISVs hold advantages such as spontaneous immune responses, low-off target toxicity, and augmented response to other immunotherapies.

d. Bioinformatics and novel antigen prediction tools

Bioinformatic tools were used to exploit NeoAgs to evaluate the probable response to ICBs in specific tumors. Moreover, these tools were developed for the identification and periodization of tumor-specific mutations. However, all the mutations do not produce neoepitopes which could be identified by the immune response [99]. Hence, HLA typing is necessary to predict epitopes with immune potential [100]. Recently, big data analysis and artificial intelligence proved advantageous in predicting neoepitope. Information for diverse human tumors comprising of HLA peptide and genomic datasets were analyzed using deep learning strategies to confirm computational models for Ag presentation. Notably, prediction tools are more precise and accurate for MHC-I in comparison to the MHC-II. It might be due to the long sequence and open ends of the letter [101,102].

CONCLUSIONS

Biology and platform-based improvements for cancer vaccines proved beneficial in improving the composition and intrinsic design of cancer vaccines respectively. Intrinsic efficacy and delivery of vaccine could be considered as major determinants of vaccine efficacy. It could be improved through biology and platform-based improvements.

However, there is much to learn about the cancer vaccine. It is the need of the hour to shift clinical trials for cancer vaccines toward immunology-oriented clinical trials. It should be noted that in the last 2 decades, many improvements have been made in the field of cancer vaccines. Clinical end-point-related improvements proved promising including tumor-specific antigens, novel antigen delivery systems, and targeting tumor microenvironments.

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Funding: Nil; Conflicts of Interest: None Stated.

How to cite this article: Bhaliya KR, Anwer M, Wei MQ. Current Strategies for the Development of a Therapeutic Cancer Vaccine – A Review. Eastern J Med Sci. 2024: Epub ahead of print.