ATJ
Advanced Therapies Journal

VOL.6 / ISSUE 18 / WINTER 2024

Online ISSN: 2676-7236

DOI: 10.22034/atj.2024.195109

OPEN ACCESS

Pages: 10-17 / Review Article / Submit: 10 Jan 2024 / Accepted: 07 March 2024

Availablein: https://www.atjournal.ir

The Bright Future of Cancer Immunotherapy: DNA Vaccines on the Front Lines Of Lung Cancer

Sahar Abareshi [1*], Yeganeh Yousefi [1], Niusha Zeynalniya Toosi [1]

[1]Department of Biology, Faculty of Science, Mashhad Branch, Islamic Azad University, Mashhad, Iran.

Corresponding Author's E-mail: Sahar74abareshi@gmail.com

Abstract:

The advancements in immuno-oncology have created a new and unparalleled opportunity for the advancement of vaccination methods. Therapeutic DNA cancer vaccines are now regarded as an excellent way to stimulate the immune system in its fight against cancer. Lung cancer is well recognized as one of the primary factors leading to patient mortality worldwide. Despite significant advancements in innovative tumor immunotherapy, including the use of immune checkpoint inhibitors or oncolytic viruses, the overall 5-year survival rate of individuals with lung malignancies remains very low. Therefore, there is an urgent need to find efficacious vaccinations for the treatment of lung cancer. DNA vaccines are now regarded as a viable immunotherapy approach to stimulate the host immune system against lung cancer. First, we discuss antigen repertoire selection and delivery strategies to improve cancer vaccines. We summarize the recent advances in DNA vaccines that target lung cancer antigens and highlight their implications for disease treatment.

Keywords: Immunotherapy, DNA vaccine, Cancer vaccine, Vaccine development

Introduction

It is essential to conquer aggressive tumors, which are the most common reason for death, to raise worldwide longevity. In 2020, there were an estimated 19.3 million new cases of cancer and nearly 10 million deaths attributable to malignancy. This emphasizes the urgent nature of this crisis (1). Traditional cancer treatments, such as as surgery, radiation therapy, and chemotherapy, can be highly hazardous and have limited effectiveness (2). This highlights the need for the development of more effective methods for treating cancer. Recent research seems to indicate a strong correlation between cancer progression and a phenomenon known as "cancer immunoediting" (3). The changing interaction suggests that the immune system may eliminate newly formed cancer cells by identifying altered oncogenic genes or promoting an immunosuppressive condition that supports tumor growth. Thus, the destiny of cancerous cells is dictated by an imbalance inside the immune system (4).

Tumor vaccination, sometimes referred to as cancer immunization or cancer immunotherapy, is a therapeutic approach aimed at activating the immune system to recognize and combat cancerous cells. The primary objective is to impede the growth, recurrence, or dissemination of tumors while enhancing the immune system's capacity to identify and eliminate malignant cells (5). Cancer vaccines work by eliciting an immune response that selectively addresses tumor-associated antigens (TAAs), which are molecules generated by cancerous cells. The

How to Cite this Article:

S. Abareshi, Y. Yousefi, N. Zeynalniya Toosi. "I The Bright Future of Cancer Immunotherapy: DNA Vaccines on the Front Lines Of Lung Cancer ", Advanced Therapies Journal ,vol. 6, no. 18, pp. 10-17, 2024.

activation of several immune cells, including T cells and B cells, triggers this immunological response, which ultimately destroys cancerous cells (6). Cancer vaccines have two main uses: preventative (to protect at-risk populations) and therapeutic (to treat patients who have already received a cancer diagnosis). Cancer vaccines have great potential as a means of preventing and treating the disease by using the immune system (7). Cancer vaccines may be categorized into four primary types: tumor-cell-based vaccinations, peptide or protein vaccines, viral-vector-based vaccines, and nucleic-acid-based vaccines (DNA or RNA vaccines) (7). Between these powerful vaccinations, DNA vaccines show great promise as immune-therapeutics for treating many types of malignancies due to their numerous benefits. DNA vaccines may stimulate both innate immune responses and effectively generate both the humoral and cell-based immunological responses of the host. Furthermore, a potent DNA vaccine may include many genes that encode tumor-specific antigens, hence enhancing immune responses against tumor antigens that play a role in tumor genesis, development, and migration (8). For instance, DNA vaccines have undergone thorough examination to create innovative approaches to combat melanoma, prostate cancer, breast cancer, and lung cancer. In addition, DNA vaccines are more convenient to produce and provide superior durability and safety in comparison to conventional vaccinations (9). Despite numerous attempts to create cancer vaccines, the therapeutic treatments including these vaccines remain relatively ineffective due to the considerable variability of tumor antigens and the limited immune system reactions they elicit. This study offers a thorough and detailed examination of the existing cancer vaccines. Initially, we outline techniques for choosing antigen repertoires and delivery technologies to enhance the creation of cancer vaccines. We provide a concise overview of the latest significant developments in the development of DNA vaccines that specifically target antigens associated with lung cancer, and discuss their importance for the management of this disease.

Cancer vaccine strategies

Cancer vaccines use many strategies to activate the body's immunity and elicit a potent anti-tumor reaction. A popular strategy includes using dendritic cells (DCs), which are very effective antigen-presenting cells (APCs). DCs may be obtained either from the blood of a person or produced in a laboratory, using one approach. Subsequently, they undergo maturation and activation by the use of immune-stimulating substances or tumor antigens (10). Following the introduction of tumor-specific antigens (TSAs) produced from tumor cells or genetic material, the loaded dendritic cells (DCs) are then delivered back to a person. The DCs move to lymphoid organs, where they engage in interactions with several types of immune cells, including T cells, B cells, and natural killer (NK) cells. The DCs display the tumor antigens to CD4+ helper T cells and CD8+ cytotoxic T lymphocytes (CTLs), resulting in their stimulation (11). Excited T cells provide stimulatory signals to other immune system cells, augmenting the body's defense against cancerous cells. CTLs particularly identify and attack cancer cells that display the tumor antigens, leading to their eradication. Furthermore, this vaccination seeks to elicit a memory answer, enabling a more efficient immune response when encountering cancer cells again in the future (11).

Peptide-based subunit vaccines, which consist of chemical and biosynthetic formulations of anticipated or confirmed individual tumor antigens, elicit a strong immune reaction targeting the specific tumor antigen location (12). A combination of peptide-based subunit vaccination and adjuvants may effectively stimulate the production of antibodies by the immune system, making it useful for both preventing and treating viral infectious illnesses. The vaccinations for liver and cervical malignancies, HBV and HPV respectively, were predominantly composed of peptide-based subunit vaccines. In the past few years, virus-like particles (VLP)-based subunit vaccines, which can stimulate cellular immunity, demonstrated significant anti-tumor efficacy (13).

Another option is using whole-cell preparations obtained from cancerous cells. Tumor cells are obtained either from the individual's tumor or from existing cell lines associated with cancer (14). These cells are rendered inactive or genetically altered to diminish their capacity to proliferate and induce illness. Upon reintroduction into the patient's body, the entire cells are identified by different immune cell types, such as DCs, macrophages, and NK cells, which initiate an immediate non-specific inflammatory reaction. Initiation of an immune response occurs when stimulated immune cells digest cancer antigens and deliver them to T cells. While CD8+ CTLs identify and destroy tumor cells expressing the given antigens, CD4+ helper T cells communicate with other immune cells to assist. Another goal of whole-cell cancer vaccines is to trigger a memory answer so that the immune system can better prevent tumor recurrence (14).

In situ, cancer vaccines are directly delivered at the tumor site or a neighboring lymph node. This strategy consists of the stimulation of antigen-presenting cells such as DCs, macrophages, neutrophils, and natural killer (NK) cells, inside the tumor microenvironment (TME) (15). The vaccination triggers an inflammatory reaction, stimulates the creation of cytokines, and attracts immune cells. Antigen-presenting cells

capture tumor antigens that are produced when the vaccination is administered, undergo the processing of these antigens, and then present them to T cells (16). CD8+ and CD4+ helper T cells are activated by this, and they collaborate to effectively eradicate tumor cells. Excited immune cells generate activator chemicals and facilitate the eradication of tumor cells inside the TME. In situ, cancer vaccines additionally strive to induce a memory reaction to enhance defenses against the reappearance of tumors (16).

The nucleic acid vaccine elicits robust CD8+ T cell responses mediated by MHC I, making it a popular choice for cancer vaccination. Nucleic acid vaccines can deliver numerous antigens at the same time, which may activate both humoral and cellular immunity. Furthermore, nucleic acid vaccines can encode whole tumor antigens, enabling antigen-presenting cells (APCs) to cross-present multiple epitopes or show multiple antigens at the same time. Ultimately, the process of creating the nucleic acid vaccine is uncomplicated and rapid, making it well-suited for the creation of individualized neoantigen cancer vaccines (17).

Several variables must be taken into account while choosing a vaccination technology. The duration necessary to create personalized vaccines is crucial in choosing vaccination platforms (18). Nucleic acid vaccines are the optimal option for some metastatic illnesses due to their ability to save time. While preparing vaccines, it is possible to utilize mixed therapies to reduce the severity of illness exacerbations and create an advantageous immunological milieu that improves immunity (19). Furthermore, while choosing a vaccine production platform, it is

important to take into account the method of use and the frequency of immunizations. Aside from selecting the appropriate platform, the optimization and design of antigens are also crucial factors. Linking tumor antigens to binding vectors (such as tetanus endotoxin or diphtheria toxoid) might enhance the ability of the antigen to stimulate an immune response (20). Utilizing protein structure, antigen-optimized design, such as virus-like particle vaccinations, has the potential to augment the immune response. Furthermore, it is essential to use bioinformatics and deep sequencing methods to facilitate vaccine design. In this study, our objective was to provide a concise overview of the most recent optimization techniques used in the development of four distinct kinds of cancer vaccines, with a particular focus on nucleic acid vaccines (20).

DNA vaccine

The fundamental idea behind cancer immunotherapy is to present different tumor antigens into the host to enhance the immune system's ability to eliminate cancer cells. Hence, the capacity of a certain medication to elicit strong immune reactions directly and significantly affects its efficacy (21). Experimental and pre-clinical trials of many immunotherapies, such as cancer vaccines, adoptive T-cell treatments, cytokine therapies, and antibody therapies, have been conducted. Among the several cancer vaccine options, DNA vaccines show the most promise for eliciting immune reactions of this magnitude. To facilitate in vivo creation and expression by the host's protein expression machinery, plasmid DNA encoding antigen and other relevant genes is introduced into the host's tissues and then transfected into the cells (22). DNA vaccines can stimulate natural immune reactions, and based on their composition and administration locations, they may also elicit humoral and cellular immune responses that are associated with particular antigens (23).

It has been demonstrated that DNA vaccines using plasmids originating from bacteria may elicit innate immune responses. It seems that the DNA of the bacterium acts as a ligand that activates Toll-like receptors (TLRs), a family of dendritic cell membrane-spanning proteins that identify molecular features related to pathogens and serve a crucial role in the innate immune system (24). The hypomethylated CpG dinucleotides pattern, which is abundant in bacterial DNA but uncommon in human DNA, reacts with TLR9 in particular. TLR9 is present in several immune cells, including dendritic cells, B cells, and natural killer cells. These cells get activated when they encounter foreign DNA, through direct transfection or phagocytosis (25). TLR9 stimulation triggers a series of inflammatory reactions, leading to the synthesis of several mediators. The localized inflammation and heightened production of cytokines resulting from the natural immune system reactions might attract and stimulate more immune cells, like lymphocytes, hence augmenting future specialized immune system reactions. Specifically, the activation of TLR9, mediated by MyD88 signaling, triggers the activation of interferon regulatory factor (IRF) 7, which in turn leads to the production of Type I interferons (IFNs) (26).

DNA vaccines serve as uncomplicated carriers for in vivo transfection and the generation of antigens. A DNA vaccine consists of a plasmid DNA that contains the genetic code for the desired antigen. This genetic code is regulated by a mammalian promoter, such as CMV-intA or CMV immediate/early promoter, together with its neighboring intron A sequence (27). The modified DNA sequence to be studied is administered to the skin (intradermally), subcutaneously, or to the muscle using several delivery mechanisms. The plasmid utilizes the cellular machinery of the host to reach

the nucleus of transfected local cells, like myocytes or keratinocytes, which also include resident APCs. In this process, the plasmid initiates the expression of genes, resulting in the production of foreign antigens. Two comprehensive models have been suggested. The plasmid encodes an antigen that is synthesized in host cells. This may occur in professional APCs, which directly stimulate immunological responses, or in nonprofessional cells. In the latter case, the antigen can be transmitted to APCs, resulting in cross-priming (28).

DNA-based vaccine administration systems

Getting DNA plasmids into the right cells and tissues is a huge hurdle for DNA vaccine researchers. To activate the host immune system and lessen certain adverse consequences, it is believed that selecting an appropriate delivery mechanism is crucial. We provide a brief overview of the current state of cancer DNA vaccine delivery systems, such as topics such as electroporation, gene-gun delivery, nanoparticle delivery, and self-assembling peptides (29). Electroporation is a well-researched method used to enhance the transfer of DNA plasmids into antigen-presenting cells (APCs). Electroporation administration enhances cell porousness by creating temporary holes, facilitating the entry of more DNA plasmids into the cells (30). Furthermore, electroporation serves as an adjuvant by attracting certain immune cells, like as dendritic cells, to the locations where DNA is injected. This, in turn, stimulates the production of proinflammatory cytokines and enhances the strength of the immune system's reaction specific to cancer proteins. Several clinical studies have examined the effectiveness of delivering the DNA vaccine by electroporation to treat diseases (31). Another frequently used method involves the use of a gene cannon to deliver a DNA vaccination, which is coated with a gold particle. This delivery technique enhances cytotoxic T-cell reactions and requires fewer DNA strands in various tests. Multiple compelling pieces of data have shown that the efficacy of cancer vaccines in combating different types of cancer, like lung cancer, may be augmented by gene gun administration. Despite their importance, electroporation and gene-gun-based delivery methods have many limitations, including the induction of significant pain upon injection and their unsuitability for widespread population immunization (31).

A novel delivery strategy has been developed to improve the absorption of certain DNA vaccines by using nanoparticle-based drug delivery systems. This innovative delivery technology can overcome the restrictions related to the movement of medications inside the body and enhance the effectiveness of pharmaceuticals that have low levels of absorption or solubility. So far, a range of nanoparticles has been used to transport DNA-based vaccines and enhance the body's immune response against tumors (32). These nanoparticles include polymeric nanoparticles, liposomes, silica nanoparticles, bisphosphonate-modified calcium phosphate nanoparticles, gold nanoparticles, virus nanoparticles, and carbon nanotubes. Self-assembling peptides (SAPs) are compact biomaterials that may serve as a very efficient drug delivery mechanism for transporting antigens to cancer cells. SAPs may be fabricated into many structures including nanomicelles, nanotubes, nanovesicles, nanotapes, and hydrogels (33). The novel delivery method has various benefits in comparison to liposomes or nanoparticles, including superior drug-loading efficiency, little drug leakage, enhanced absorption, and exceptional biodegradability. In addition, it may stimulate a long-lasting immunological response without the need for an adjuvant, as stated in reference (33). Recent research demonstrated the efficacy of a novel delivery platform, known as Glycosaminoglycan (GAG)-binding enhanced transduction (GET), in facilitating the transfer of nucleic acids for gene therapy in lung organs. The tripeptide binds to the DNA plasmids, forming complexes with them. These complexes are then encapsulated in nanoparticles. The nanoparticles may be transported to different organs, with a particular focus on the lungs. This method shows promising promise for delivering DNA vaccines. However, the primary disadvantage linked to low pH in superabsorbent polymers (SAPs) is the necessity for enhancement (34).

Cancer DNA vaccines advantages and limitations

The utilization of DNA as a means of vaccination was initiated during the 1990s. This involved the introduction of a plasmid DNA that contained the genetic code for the influenza A nucleoprotein. As a result, a targeted and effective immune response was triggered, namely involving CTLs (35). Subsequently, DNA vaccines have been created to address a range of conditions, such as allergies, infectious disorders, autoimmune diseases, and cancer. DNA vaccines utilize bacterial plasmids to carry genetic information for antigens and immunostimulatory substances such as IL-2 and GM-CSF (36). They can be administered through several methods, such as intramuscular (IM), intradermal (ID), subcutaneous (SC), and mucosal. Physical approaches, including electroporation, sonoporation, DNA tattooing, or gene guns, are frequently employed for delivering DNA to the nucleus (37). These techniques effectively bypass obstacles within and outside the cell to transport DNA. Upon entering the nucleus, the antigen coded by the DNA vaccine must be produced and displayed on major histocompatibility molecules (MHC) to

activate T cells. A significant benefit of DNA vaccines is their ability to convey the encoded antigen through MHC class I and class II, thereby stimulating both CD4 and CD8 T cells and, informally, humoral immunity (38). Moreover, the inherent components of plasmid DNA might potentially trigger the natural immune reaction as a result of the identification of the double-stranded DNA structure by cytosolic sensors. Mouse models have shown the successful activation of a targeted and effective immune response against many antigens and tumor-associated antigens in various cancer types (39). Cancer DNA vaccines provide benefits over nonspecific and nontargeted medicines in terms of antigen sensitivity and security. Unlike these treatments, which may have numerous adverse effects and cause significant harm to healthy tissues, DNA vaccines are more targeted and pose less risk. Cancer DNA vaccines elicit a systemic immune response, making them efficient against metastatic tumors, which are resistant to surgical removal. Furthermore, DNA vaccines differ from antibodies and small molecule inhibitors in that they stimulate the development of immune system memory (40).

Nevertheless, regardless of advancements in delivery methods, DNA vaccines exhibited suboptimal immunogenicity throughout human studies. Various molecular techniques, including codon optimization, have been experimented with to enhance their effectiveness (41). This gene engineering strategy allows for the substitution of synonymous codons to enhance protein synthesis and plasmid immunity. Cancer optimization DNA vaccines have shown high effectiveness in several preclinical models, particularly in preventive settings, and have established a strong safety profile in people. Regrettably, the efficacy of medicinal vaccination remains restricted, even in preclinical studies (42). The drawback primarily arises from the different kinds of resistance that occur throughout tumor growth. These processes include the loss or alteration of epitopes that immune cells understand, T cell exhaustion, antigen tolerance, and the infiltration of immunosuppressive cells including regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages (TAMs). These cells generate suppressive cytokines like TGF-β and IL-10 and also contribute to a deprivation of nutrients and oxygen (41). Therefore, it is essential to develop novel techniques to fully eliminate malignancies. Upon analyzing the most recent 5-10 years of experimental and clinical studies, two primary patterns emerged. Choosing the appropriate encoded antigen(s) for a DNA vaccine might enhance its potency and stimulate a wide-ranging immune system reaction, therefore addressing issues related to epitope loss, alterations, and resistance. Furthermore, the implementation of techniques that integrate several treatments has been carried out to hinder the penetration of immunosuppressive cells and the generation of suppressive cytokines, to diminish suppression inside the tumor microenvironment (43).

The mechanisms by which lung cancer DNA vaccines engage the immune system

Lung cancer is now the primary cause of cancer mortality globally. Despite several recent advancements, the annual incidence of lung cancer exceeds 2 million cases, with a rising prevalence among those who do not smoke and women. Non-small cell lung cancer (NSCLC) accounts for around 85% of newly detected instances of lung cancer, with almost all patients being identified with advanced-stage illness (44). Significant advancements have been made in the last ten years regarding the management of NSCLC, mostly due to the emergence of specific medicines and immunotherapy. Immune checkpoint inhibitors (ICIs) are currently the primary therapy for severe non-small cell lung cancer (NSCLC), with some patients experiencing unprecedented responses and extended life, which was not previously seen in the context of metastatic NSCLC (45). Nevertheless, it is important to note that not all patients have a sustained positive outcome when treated with immune checkpoint inhibitors (ICIs). The crucial factor for a successful response appears to be the penetration of T-cells that can identify and eliminate cancer cells. Data indicates that immune checkpoint inhibitors (ICIs) are less effective in "cold tumors," which are characterized by a deficiency of T-cell infiltration. Additional measures are required to enhance the clinical results, expanding the advantages to a larger number of individuals while minimizing needless exposure for those who are unlikely to get any sort of advantage (46).

The fundamental idea behind a DNA vaccine for lung cancer is to deliver promising and efficient tumor antigens into the host, therefore stimulating the host's immune system to eliminate tumor cells. To develop a potent DNA vaccination for lung cancer, the genes that encode particular tumor antigens or immunostimulatory elements are inserted into a plasmid that can be expressed in eukaryotic cells. The vaccinations may be administered to the host by many immunization methods, such as intramuscular, intradermal, transcutaneous, and mucosal injections (47). Furthermore, the DNA plasmids may be introduced into the cells by mechanical processes such as electroporation, sonoporation, or gene gun. Upon uptake of the plasmid, the target cell proceeds to produce the desired antigen and then offers it to lymphocytes via the signaling pathways of the major histocompatibility complex (48). Subsequently, the foreign antigens are shown to MHC class II molecules and instruct CD4+ T cells to stimulate the production

of tumor-antigen-specific antibodies. Similarly, the acquired foreign substances can be transmitted to MHC class I molecules and trigger targeted cellular immune reactions by engaging with CD8+ cytotoxic T cells, which is crucial for eliminating cancerous cells. The ability to combat cancer greatly relies on the effectiveness of the particular CD8+ T cell-induced immunity (49). DNA vaccines are very efficient in stimulating CD8+ T cell responses. Currently, there are just two cancer vaccines that have been authorized for use in humans, namely Sipuleucel T and T-VEC. Sipuleucel-T (Provenge) was the first dendritic-cell-based cancer vaccine sanctioned by the U.S. Food and Drug Administration (FDA) to manage prostate carcinoma. T-VEC (talimogene laherparepvec) was the pioneering oncolytic viral vaccine for treating those suffering from melanoma (50). Noteworthy preclinical research showed that a genetically modified DNA vaccination effectively reduced tumor nodules and had strong anticancer effects in a mouse model of lung cancer. Despite the shown ability of DNA vaccines to generate beneficial immune responses against tumors, the development of DNA vaccines specifically for lung cancer is now limited to clinical trials. Advancements in the delivery and optimization of DNA plasmids will enhance the effectiveness of DNA vaccines in clinical trials, hence facilitating their implementation in patients for translational purposes (51).

Lookahead Possibilities

Based on an examination of current experimental and clinical studies, it appears improbable that the existing curative cancer vaccines, when used in isolation, would have a substantial influence on cancer results. Extensive testing of combinations with different approaches has revealed that the combined approach exhibits a more substantial capacity for enhancing clinical results in comparison to the individual treatment. Personalized methods will be critical for clinical achievement, encompassing both the creation of vaccines and the selection of combination therapies. In addition, given the safety and tolerability of DNA vaccines, their integration with other therapeutic approaches may eventually become the norm for the treatment of numerous cancers. DNA vaccines represent a paradigm shift in immunotherapy, integrating the principles of precision medicine and immunoenhancement. They can provide an approach to therapy for a large number of malignancies, such as lung cancer, in the context of DNA vaccines. DNA vaccines, notwithstanding the noteworthy advancements observed in cancer studies, encounter certain constraints and difficulties during clinical studies. These include inadequate immunogenicity in human subjects, restricted applicability to protein immunogens, and the induction of passable antibody production against DNA. Moreover, immunologic tolerance and early designs of DNA vaccines are the primary reasons for their lack of success in human clinical studies. Efforts have been made in recent times to augment the host's immune response against lung cancer through the incorporation of innovative immunological adjuvants, including cytokines and chemokines, as well as TAAs or TSAs. While intramuscular injections are a prevalent method for administering DNA vaccines, device-mediated vaccinations, particularly electroporation and gene guns, remain a prevalent approach. Molecular adjuvant-based DNA vaccines and nanoparticle-based delivery systems have also demonstrated enhanced potential for effectiveness in a multitude of ongoing research studies. The latest clinical studies suggest that the present cancer vaccines are inadequate in producing optimal results alone via a single component. Hence, the integration of additional tactics, such as incorporating innovative adjuvants and delivery platforms, will enhance the clinical results in comparison to using a single treatment. Moreover, the use of a customized approach in the creation of DNA vaccines would be crucial for achieving success in clinical applications. To effectively treat patients with lung cancer with DNA vaccine vaccination, more comprehensive research is required in the future.

Acknowledgements

The authors would like to thank the Department of Biology, Faculty of Science, Mashhad Branch, Islamic Azad University, Mashhad, Iran. for their support.

Authors' Contribution

Sahar Abareshi and Yeganeh Yousefi and Niusha Zeynalniya Toosi were involved in the conceptualization, design, and support of the study. All authors read and confirmed the final manuscript.

Funding

Not applicable.

Availability of data and materials

All data are obtainable after an appeal from the corresponding author.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare they have no conflicts of

interest regarding the publication of this article.

References

1. Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians, 71(3), 209-249.
2. Fan, T., Zhang, M., Yang, J., Zhu, Z., Cao, W., & Dong, C. (2023). Therapeutic cancer vaccines: advancements, challenges, and prospects. Signal Transduction and Targeted Therapy, 8(1), 450.
3. Mirzayans, R., & Murray, D. (2022). What are the reasons for continuing failures in cancer therapy? Are misleading/inappropriate preclinical assays to be blamed? Might some modern therapies cause more harm than benefit?. International Journal of Molecular Sciences, 23(21), 13217.
4. Schreiber, R. D., Old, L. J., & Smyth, M. J. (2011). Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. Science, 331(6024), 1565-1570
5. Kaczmarek, M., Poznańska, J., Fechner, F., Michalska, N., Paszkowska, S., Napierała, A., & Mackiewicz, A. (2023). Cancer vaccine therapeutics: limitations and effectiveness—A literature review. Cells, 12(17), 2159.
6. Faghfuri, E., Pourfarzi, F., Faghfouri, A. H., Abdoli Shadbad, M., Hajiasgharzadeh, K., & Baradaran, B. (2021). Recent developments of RNA-based vaccines in cancer immunotherapy. Expert opinion on biological therapy, 21(2), 201-218.
7. Huang, T., Liu, L., Lv, Z., Zhao, K., Yi, Q., & Zhang, J. (2022). Recent advances in DNA vaccines against lung cancer: A mini review. Vaccines, 10(10), 1586.
8. Huang, T., Song, X., Jing, J., Zhao, K., Shen, Y., Zhang, X., & Yue, B. (2018). Chitosan-DNA nanoparticles enhanced the immunogenicity of multivalent DNA vaccination on mice against Trueperella pyogenes infection. Journal of nanobiotechnology, 16, 1-15.
9. Huang, T., Zhao, K., Song, X., Song, T., Wang, X., Zhang, X., ... & Chu, Y. (2022). Heterologous prime-boost immunization with dna vaccine and modified recombinant proteins enhances immune response against Trueperella pyogenes in mice. Vaccines, 10(6), 839.
10. Liu, J., Fu, M., Wang, M., Wan, D., Wei, Y., & Wei, X. (2022). Cancer vaccines as promising immuno-therapeutics: platforms and current progress. Journal of Hematology & Oncology, 15(1), 28.
11. Huang, T., Zhao, K., Song, X., Song, T., Wang, X., Zhang, X., ... & Chu, Y. (2022). Heterologous prime-boost immunization with dna vaccine and modified recombinant proteins enhances immune response against Trueperella pyogenes in mice. Vaccines, 10(6), 839.
12. Melief, C. J., van Hall, T., Arens, R., Ossendorp, F., & van der Burg, S. H. (2015). Therapeutic cancer vaccines. The Journal of clinical investigation, 125(9), 3401-3412.
13. Fu, C., Zhou, L., Mi, Q. S., & Jiang, A. (2020). DC-based vaccines for cancer immunotherapy. Vaccines, 8(4), 706.
14. Keenan, B. P., & Jaffee, E. M. (2012, June). Whole cell vaccines—past progress and future strategies. In Seminars in oncology (Vol. 39, No. 3, pp. 276-286). WB Saunders.
15. Viswanath, D. I., Liu, H. C., Huston, D. P., Chua, C. Y. X., & Grattoni, A. (2022). Emerging biomaterial-based strategies for personalized therapeutic in situ cancer vaccines. Biomaterials, 280, 121297.
16. Hammerich, L., Binder, A., & Brody, J. D. (2015). In situ vaccination: Cancer immunotherapy both personalized and off-the-shelf. Molecular oncology, 9(10), 1966-1981.
17. Restifo, N. P., Ying, H., Hwang, L., & Leitner, W. W. (2000). The promise of nucleic acid vaccines. Gene therapy, 7(2), 89-92.
18. Khodaei, T., Sadri, B., Nouraein, S., Vahedi, N., & Mohammadi, J. (2020). Cancer vaccination: Various platforms and recent advances. J. Immun. Biol, 5, 151.
19. Vergati, M., Intrivici, C., Huen, N. Y., Schlom, J., & Tsang, K. Y. (2010). Strategies for cancer vaccine development. BioMed research international, 2010.
20. Kudrin, A. (2012). Overview of cancer vaccines: Considerations for development. Human vaccines & immunotherapeutics, 8(9), 1335-1353.
21. Yang, B., Jeang, J., Yang, A., Wu, T. C., & Hung, C. F. (2014). DNA vaccine for cancer immunotherapy. Human vaccines & immunotherapeutics, 10(11), 3153-3164.
22. Liu, S., Jiang, Q., Zhao, X., Zhao, R., Wang, Y., Wang, Y., ... & Ding, B. (2021). A DNA nanodevice-based vaccine for cancer immunotherapy. Nature Materials, 20(3), 421-430.
23. Lu, S., Wang, S., & Grimes-Serrano, J. M. (2008). Current progress of DNA vaccine studies in humans. Expert review of vaccines, 7(2), 175-191.
24. Lopes, A., Vandermeulen, G., & Préat, V. (2019). Cancer DNA vaccines: current preclinical and clinical developments and future perspectives. Journal of Experimental & Clinical Cancer Research, 38, 1-24.
25. Stevenson, F. K., Ottensmeier, C. H., Johnson, P., Zhu, D., Buchan, S. L., McCann, K. J., ... & Rice, J. (2004). DNA vaccines to attack cancer. Proceedings of the National Academy of Sciences, 101(suppl_2), 14646-14652.
26. Morse, M. A., Gwin III, W. R., & Mitchell, D. A. (2021). Vaccine therapies for cancer: then and now. Targeted oncology, 16(2), 121-152.
27. Franck, C. O., Fanslau, L., Bistrovic Popov, A., Tyagi, P., & Fruk, L. (2021). Biopolymer-based carriers for DNA vaccine design. Angewandte Chemie International Edition, 60(24), 13225-13243.
28. Eusébio, D., Neves, A. R., Costa, D., Biswas, S., Alves, G., Cui, Z., & Sousa, Â. (2021). Methods to improve the immunogenicity of plasmid DNA vaccines. Drug Discovery Today, 26(11), 2575-2592.
29. Soltani, S., Farahani, A., Dastranj, M., Momenifar, N., Mohajeri, P., & Emamie, A. D. (2018). DNA vaccine: Methods and mechanisms. Advances in Human Biology, 8(3), 132-139.
30. Stevenson, F. K., Ottensmeier, C. H., Johnson, P., Zhu, D., Buchan, S. L., McCann, K. J., ... & Rice, J. (2004). DNA vaccines to attack cancer. Proceedings of the National Academy of Sciences, 101(suppl_2), 14646-14652.
31. Rezaei, T., Davoudian, E., Khalili, S., Amini, M., Hejazi, M., de la Guardia, M., & Mokhtarzadeh, A. (2021). Strategies in DNA vaccine for melanoma

cancer. Pigment cell & melanoma research, 34(5), 869-891.
32. Hasson, S. S. A. A., Al-Busaidi, J. K. Z., & Sallam, T. A. (2015). The past, current and future trends in DNA vaccine immunisations. Asian Pacific Journal of Tropical Biomedicine, 5(5), 344-353.
33. Coban, C., Koyama, S., Takeshita, F., Akira, S., & Ishii, K. J. (2008). Molecular and cellular mechanisms of DNA vaccines. Human vaccines, 4(6), 453-457.
34. Shah, M. A. A., He, N., Li, Z., Ali, Z., & Zhang, L. (2014). Nanoparticles for DNA vaccine delivery. Journal of biomedical nanotechnology, 10(9), 2332-2349.
35. Lopes, A., Vandermeulen, G., & Préat, V. (2019). Cancer DNA vaccines: current preclinical and clinical developments and future perspectives. Journal of Experimental & Clinical Cancer Research, 38, 1-24.
36. Pandya A, Shah Y, Kothari N, Postwala H, Shah A, Parekh P, Chorawala MR. The future of cancer immunotherapy: DNA vaccines leading the way. Med Oncol. 2023 Jun 9;40(7):200
37. Gary, E. N., & Weiner, D. B. (2020). DNA vaccines: prime time is now. Current Opinion in Immunology, 65, 21-27.
38. Morse, M. A., Gwin III, W. R., & Mitchell, D. A. (2021). Vaccine therapies for cancer: then and now. Targeted oncology, 16(2), 121-152.
39. Ori, D., Murase, M., & Kawai, T. (2017). Cytosolic nucleic acid sensors and innate immune regulation. International reviews of immunology, 36(2), 74-88.
40. Denies, S., Cicchelero, L., Polis, I., & Sanders, N. N. (2016). Immunogenicity and safety of xenogeneic vascular endothelial growth factor receptor-2 DNA vaccination in mice and dogs. Oncotarget, 7(10), 10905.
41. Suschak, J. J., Williams, J. A., & Schmaljohn, C. S. (2017). Advancements in DNA vaccine vectors, non-mechanical delivery methods, and molecular adjuvants to increase immunogenicity. Human vaccines & immunotherapeutics, 13(12), 2837-2848.
42. Jorritsma, S. H. T., Gowans, E. J., Grubor-Bauk, B., & Wijesundara, D. K. (2016). Delivery methods to increase cellular uptake and immunogenicity of DNA vaccines. Vaccine, 34(46), 5488-5494.
43. Lambricht, L., Vanvarenberg, K., De Beuckelaer, A., Van Hoecke, L., Grooten, J., Ucakar, B., ... & Vandermeulen, G. (2016). Coadministration of a plasmid encoding HIV-1 gag enhances the efficacy of Cancer DNA vaccines. Molecular Therapy, 24(9), 1686-1696.
44. García-Pardo, M., Gorria, T., Malenica, I., Corgnac, S., Teixidó, C., & Mezquita, L. (2022). Vaccine therapy in non-small cell lung cancer. Vaccines, 10(5), 740.
45. Lahiri, A., Maji, A., Potdar, P. D., Singh, N., Parikh, P., Bisht, B., ... & Paul, M. K. (2023). Lung cancer immunotherapy: progress, pitfalls, and promises. Molecular cancer, 22(1), 40.
46. Saab, S., Zalzale, H., Rahal, Z., Khalifeh, Y., Sinjab, A., & Kadara, H. (2020). Insights into lung cancer immune-based biology, prevention, and treatment. Frontiers in immunology, 11, 502465.
47.Porter, K. R., & Raviprakash, K. (2017). DNA vaccine delivery and improved immunogenicity. Current issues in molecular biology, 22(1), 129-138.
48. Freeman-Keller, M., Goldman, J., & Gray, J. (2015). Vaccine immunotherapy in lung cancer: clinical experience and future directions. Pharmacology & Therapeutics, 153, 1-9.
49. Mellstedt, H., Vansteenkiste, J., & Thatcher, N. (2011). Vaccines for the treatment of non-small cell lung cancer: investigational approaches and clinical experience. Lung cancer, 73(1), 11-17.
50. Oliveres, H., Caglevic, C., Passiglia, F., Taverna, S., Smits, E., & Rolfo, C. (2018). Vaccine and immune cell therapy in non-small cell lung cancer. Journal of thoracic disease, 10(Suppl 13), S1602.
51. Weng, T. Y., Yen, M. C., Huang, C. T., Hung, J. J., Chen, Y. L., Chen, W. C., ... & Lai, M. D. (2014). DNA vaccine elicits an efficient antitumor response by targeting the mutant Kras in a transgenic mouse lung cancer model. Gene therapy, 21(10), 888-896.