A Comprehensive Review of Nanoadjuvants in Cancer Vaccines and Their Immunomodulatory Role and Clinical Applications

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Abstract

Cancer vaccines could potentially stimulate the immune system to target and eliminate cancerous cells by stimulating the immune system. Treatment options include surgery, chemotherapy, radiation therapy, immunotherapy, and targeted therapy, depending on the type and stage of cancer. Several challenges must be overcome to achieve an effective and long-lasting immune response. Nanoadjuvants have emerged as an essential component of cancer vaccines for their ability to improve antigen delivery, increase immunogenicity, and modulate the immune response to a given antigen. The current review details the latest developments in nanoadjuvants for cancer vaccines. Nanoparticles such as liposomes, polymeric nanoparticles, and metallic nanostructures have been shown to have a unique ability to enhance the effectiveness of vaccines by facilitating antigen uptake, stimulating dendritic cell maturation, and inducing a robust immune response mediated by T cells. It is also possible, with nanoadjuvants, to engineer and develop immunoadjuvants that release antigens in a controlled manner. This enhances the immune response duration and specificity for an extended period. Moreover, the review discusses the potential application of nanoadjuvants in highly customized cancer vaccines, in which the nanoformulation has been designed to match the specific antigens of the patient's tumors. In numerous preclinical and clinical studies, nanoadjuvant-based cancer vaccines have been evaluated for their safety and effectiveness, and various formulations are currently being tested at different stages of development to determine their efficacy and safety. However, despite these advances, several challenges still remain, such as potential toxicity, scaling up production, and overcoming regulatory hurdles, despite these advancements. In conclusion, by giving an overview of the future directions of nanoadjuvants in cancer immunotherapy, and emphasizing the need for

interdisciplinary collaborative efforts to address these challenges to fully unlock the potential of this innovative approach to cancer immunotherapy.

Keywords: Nanoadjuvants, cancer vaccines, nanoparticles, immune response, cancer immunotherapy

1. Context

A vaccine is widely recognized as one of the most effective ways to prevent and treat disease and has been used for a very long time to combat infectious diseases worldwide. Recently, this approach has been applied to a broad range of new applications, including cancer treatment (1). Cancer is one of the most critical diseases worldwide, and several strategies have been used to fight against it, and immunotherapy is employed as one of the best techniques (2, 3). Vaccines against cancer serve to stimulate the body's immune system to recognize and destroy cancer cells when they are injected into it (4). While infectious vaccines, which have been associated with wide dissemination over the past few decades, often face several obstacles, such as the inherent absence of a robust and sustained immune response, cancer vaccines are not as successful as infectious vaccines (5). In most cases, these problems are caused by cancer antigens, which cannot generate strong immune responses, and thus, they cannot stimulate the immune system as they should (6). Cancer cells are naturally recognized by the body's immune system and destroyed by it as soon as they become abnormal cells. Despite this, cancer cells may be able to escape the immune response since they are similar to the cells of the body that are not cancerous (7). There is also a tendency for tumor microcellular environments to be regulated in such a way as to suppress immune reactions. The lack of these characteristics makes cancer vaccines alone incapable of eliciting an immune response that is effective against cancer. Hence, it is a matter of great concern that more and more research is being done so that it is possible to make cancer vaccines more effective.

Adjuvants are one of the most important strategies that can be used to enhance immune responses against cancer antigens. An adjuvant is a substance added to antigens in vaccine formulations to enhance the immune response to these antigens. As a conventional vaccine, aluminum and oil emulsions are widely used as adjuvants in order to enhance the immune response. Despite this,

these compounds tend to be ineffective in fighting cancer antigens and cause weak immune responses in the body. This has caused the need for new and more effective adjuvants in cancer vaccines. Meanwhile, nanotechnology has been proposed as an innovative and powerful tool to improve cancer treatment and diagnosis (8, 9). Nanoadjuvants are nanoscale materials that carry cancer antigens and deliver them to specific body areas. These nanoparticles' small size and large surface area allow them to interact directly with the immune system. This creates a stronger immune response. In addition, nanoadjuvants optimize structure and function to interact with cancer antigens and enhance immune responses precisely (10).

2. Data acquisition

Nanoadjuvants can improve immune responses through various mechanisms. One of these mechanisms is the controlled delivery of antigens to dendritic cells (11). Dendritic cells serve as the main presenters of antigens to T cells and play a central role in the stimulation of immune responses. Nanoadjuvants are able to deliver cancer antigens to these cells in a targeted manner and increase the efficiency of immune responses. In addition, nanoadjuvants can enhance innate and acquired immune responses by activating inflammatory pathways and producing cytokines (12, 13).

Another advantage of using nanoadjuvants is reducing the required vaccine dose and side effects (14). By using nanoparticles, antigens can be delivered in a concentrated form and with a lower dose, thus reducing unwanted side effects. Also, nanoadjuvants can protect vaccines against premature degradation in the body and increase their stability and efficiency (15).

Although nanoadjuvants have shown promising results in preclinical stages and early studies, there are still many challenges for this technology to enter the clinical arena. One of these challenges is nanoparticle safety and toxicity issues (16). More research must ensure that these nanoscale materials do not accumulate in the body in the long term and cause serious side effects. In addition, developing efficient methods for producing and scaling these nanoadjuvants is another one of the existing challenges. Despite these challenges, nanoadjuvants are recognized as one of the most important new tools in developing cancer vaccines, and more research is being done in this field (17). Advances in this field can lead to significant improvements in the effectiveness of cancer vaccines and increased survival rates in cancer patients. Combining the knowledge of nanotechnology and immunology can open new horizons in cancer treatment, and nanoadjuvants will play a key role in realizing this goal (18). This review aims to explore the role of nanoadjuvants in cancer vaccines, highlighting their potential to enhance immune responses and improve vaccine efficacy. It seeks to examine the immunomodulatory mechanisms of various nanoadjuvants and their impact on antigen presentation, T-cell activation, and immune memory. Additionally, this review aims to discuss the clinical applications of nanoadjuvant-based cancer vaccines, analyzing current advancements, challenges, and future prospects in cancer immunotherapy.

3. Mechanisms of Action of Nanoadjuvants in Modulating Immune Responses

Using the unique properties of nanoparticles as adjuvants, nanoadjuvants create an immunostimulatory effect by regulating and enhancing immune response. It is important to appreciate that targeting antigen delivery to the immune system is one of these nanoparticles' most important mechanisms of action (19). Nanoadjuvants are easily absorbed by immune cells because

of their small size and large surface area, making them highly effective in interacting with them (20). In addition, dendritic cells play an important role in capturing antigens, processing them, and presenting them to T cells (21). As a result of nanoadjuvants, antigens are directly transferred to these cells, which increases the presentation of these antigens. Nanoadjuvants activate dendritic cells by presenting antigens to them so that they can recognize the antigen. Dendritic cells mature after absorbing nanoparticles and antigens and produce cytokines and stimulatory molecules, stimulating T cells (22). Activating T cells is one of the main goals of cancer vaccines because these cells recognize and destroy cancer cells. Nanoadjuvants create a more effective immune response by creating a favorable environment for activating dendritic cells and, thus, promoting T cells (23).

In addition to directly stimulating dendritic cells and T cells, nanoadjuvants also induce innate immune responses. Nanoparticles activate innate immune system signaling pathways, leading to interferons and inflammatory cytokines (24). These cytokines are essential for strengthening acquired immune responses and provide a suitable environment for stimulating and increasing immune cells (25). In particular, nanoadjuvants can activate pathways such as Toll-like receptors (TLRs), which stimulate innate and acquired immune responses. Nanoadjuvants enhance B cell responses and antibody production. Humoral immune responses, including B-cell antibody production, are critical to long-term immunity and fighting cancer cells (26). By presenting antigens to B cells and improving their interaction with T helper cells, nanoadjuvants increase antigen-specific antibody production. These antibodies bind to cancer cells and mark them for destruction by other immune cells (27).

Developing immune memory is one of the basic goals of any vaccine, and nanoadjuvants play a significant role in creating this immune memory. By enhancing primary immune responses,

nanoparticles activate memory T and B cells (28). These memory cells remain in the body after initial exposure to the antigen. In case of re-exposure to cancer antigens, they generate a faster and stronger immune response (29). Creating this immune memory can lead to lasting effects of cancer vaccines and reduce the possibility of disease recurrence. Nanoadjuvants can also change the microcellular environment of tumors and make it more suitable for immune system activity (30). In many tumors, the microcellular environment is immunosuppressive, and immune cells cannot penetrate and destroy cancer cells. Nanoadjuvants can improve immune cell penetration and activity conditions by stimulating cytokine production and changing cells' composition in the tumor environment (31). This increases the penetration of killer T cells into the tumor and increases the rate of cancer cell destruction.

It must also consider that nanoadjuvants possess unique physical, chemical, and biological properties. This makes them effective carriers for transporting pharmaceutical compounds or immunomodulatory molecules (32). In addition to delivering antigens to the patient, nanoadjuvants can simultaneously deliver small molecules that inhibit or stimulate the immune system. This affects multiple immune pathways simultaneously (33). This is one of the biggest advantages of nanoadjuvants, which improve the efficacy of cancer vaccines, regulate immune responses, and target immune responses precisely (34). Nanotechnology techniques allow nanoparticles with specific physical and chemical properties to target specific cells and tissues in the body. This allows researchers to deliver nanoadjuvants to tumor or lymph node sites precisely, maximizing cancer vaccine efficacy (35). This fine-tuning results in fewer side effects and a stronger and more stable immune response (Figure 1).

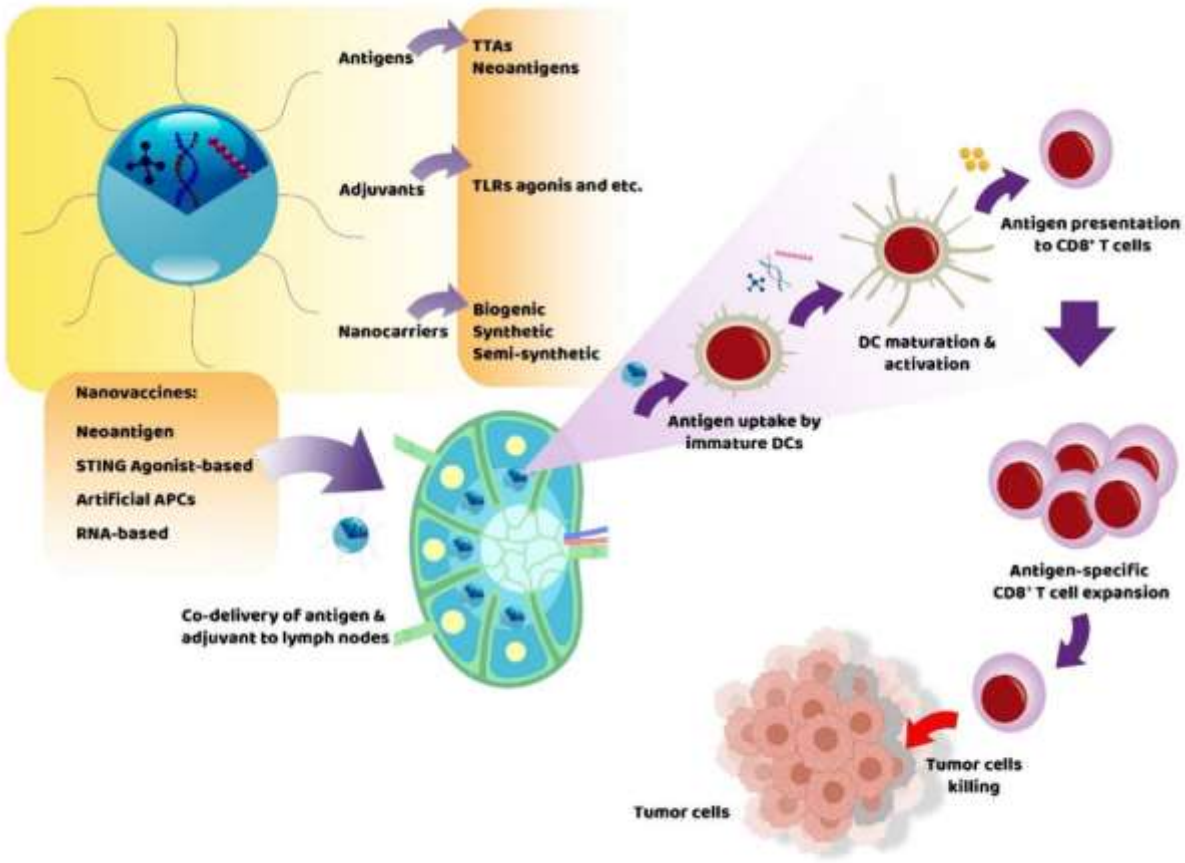

Figure 1. Nanovaccines in the treatment of cancer. The general structure of nanovaccines, their types, and the mechanism of action of this type of vaccine is shown. After the administration of nanovaccine and the delivery of antigens and adjuvants to lymphoid tissues, antigens are uptake by DCs, resulting in DCs maturation and activation. After this stage, the matured DCs present the antigens to the CD8+ T cells through the MHC molecules and cause T cell expansion. Finally, antigen-specific T cells invade and kill tumor cells in the TME. APC: antigen-presenting cell; DC: dendritic cell; TAAs: tumor-associated antigens; TLR: Toll-like receptor (36).

4. Preclinical Studies and Experimental Models

The results of preclinical studies play a crucial role in determining the efficacy and safety of nanoadjuvant therapy in cancer vaccines. Animal models are mainly used to conduct these studies, allowing researchers to test nanoadjuvant immunogenic effects on living organisms during complex research. Several animal models have been developed, such as lab mice, that can be used to study cellular and humoral immune responses to cancer vaccines (37). This is because their immune structures are similar to the human immunological system. It is possible to determine how nanoparticles are transported, how DCs absorb them, and whether or not it is possible to enhance immunological responses against tumors through preclinical studies (38). In terms of preclinical studies, one of the most important benefits of using animal models is that researchers can determine whether nanoadjuvants can simultaneously affect both adaptive and innate immune responses, one of the most critical components of preclinical research (27). It has been demonstrated in long-term studies that certain nanoadjuvants, in addition to enhancing killer T cells, may also reduce the number of regulatory T cells, which generally cause immunosuppression in animal tumor models (39). These changes can change the microcellular environment of the tumor in favor of the immune response and ultimately increase the probability of tumor regression. Such results in animal models indicate the high potential of these nanoadjuvants to enhance cancer vaccine effectiveness in humans.

Various animal models evaluate nanoadjuvant performance in cancer vaccines, including mouse models, dog models, and even non-human models such as monkeys. The advantages and disadvantages of each of these models can be found in their descriptions (40). Regarding preclinical models, mice are among the most popular because of their easy accessibility and low cost. However, it would be best to remember that some of the observed responses may not be fully reproducible in humans due to significant differences in the immune system between mice

and humans (41). A large animal model, such as dogs and monkeys, can provide more accurate results because their immune systems are more similar to humans than smaller animals. Even though they are more complex and expensive, they are also more suitable. Several recent preclinical studies on mice models have shown that nanoadjuvants can significantly increase the survival rates of mice carrying tumors (42, 43). Among the studies, one of the most successful and exciting studies was using a nanoadjuvant based on lipid nanoparticles in combination with tumor antigens to treat mice with melanoma. This nanoadjuvant induced an increase in the proliferation of killer T cells at the site of the tumor, according to the results of this study. The process also resulted in a stable immune memory, which prevented the tumor from regrowing in the long run. Based on these results, nanoadjuvants can produce lasting immunity against cancer tumors even when administered as a single dose.

In addition to evaluating their effectiveness, preclinical studies also investigate the safety and toxicity of nanoadjuvants (44). Although nanoparticles can quickly spread in the body due to their small size and unique properties, these properties can lead to their accumulation in sensitive organs such as the liver and kidneys. Animal studies have shown that nanoparticle accumulation in specific tissues can cause inflammation and cell damage. Therefore, it is necessary to investigate the toxicity of nanoadjuvants in animal models to evaluate their safety and optimal dosage and avoid side effects in clinical studies (45). Tumor models in preclinical studies can be used in two ways: xenograft and induced tumor models. Cancer cells are transplanted directly into animal bodies in transplanted tumor models. In induced tumor models, chemical or genetic agents are applied to create the tumor. Each of these models responds differently to nanoadjuvants. Transplantation tumor models are more widely used due to their ease of establishment and faster

reaction control. Still, induction tumor models can provide more realistic results due to their greater similarity to the body's natural tumor formation process (46).

Preclinical studies on nanoadjuvants are often conducted in combination with other immunotherapies (47). For example, some studies have shown that combining nanoadjuvants with immune inhibitors such as anti-PD-1 or anti-CTLA-4 can strongly enhance the immune response to tumors. These compounds effectively prevent immune suppression by tumors and increase killer T cell penetration into the tumor. These combined approaches can ultimately lead to more effective treatment strategies that are safer and more effective than traditional methods. Overall, preclinical studies on nanoadjuvants provide valuable information about their mechanisms of action, safety, and efficacy in animal models. These studies provide the necessary foundations to enter clinical phases (48). They can help researchers design more efficient and safer nanoadjuvants for cancer vaccines. However, due to the differences between animal and human immune systems, preclinical results should be interpreted cautiously. Their confirmation in human experimental studies is essential. Such an approach can ensure the successful transfer of nanoadjuvants to clinical applications (Table 1).

Table 1. This table provides multiple nanoadjuvants for each cancer type, covering a variety of materials and their unique properties in the context of cancer immunotherapy.

Type of Cancer	Type of Nanoadjuvant	Property
Melanoma	Lipid-based nanoparticles	Enhanced antigen delivery and immune activation.
	Gold nanoparticles	Stability and adjuvant activity with strong immune response.
	PLGA nanoparticles	Biodegradable and controlled antigen release.
	Gold nanoparticles	Enhanced targeting and immune activation.

Breast Cancer	Polymer-based nanoparticles (PLGA)	Controlled and sustained antigen release, low toxicity.
	Liposomal nanoparticles	Efficient antigen encapsulation and enhanced immune response.
Lung Cancer	Chitosan nanoparticles	Mucoadhesion and enhanced pulmonary delivery.
	Carbon nanotubes	Targeted delivery and immune stimulation.
	Mesoporous silica nanoparticles	High surface area for antigen adsorption and immune activation.
Prostate Cancer	PLGA nanoparticles	Controlled release and enhanced antigen delivery.
	Gold nanoparticles	Improved targeting and immune system activation.
	Iron oxide nanoparticles	Magnetic properties for enhanced targeting and immune response.
Colorectal Cancer	Dendrimers	Multivalent antigen presentation and immune stimulation.
	Silica nanoparticles	Stability in biological systems and immune activation.
	Polymeric micelles	Enhanced solubility and adjuvant effect.
Pancreatic Cancer	Carbon nanotubes	Targeted delivery and antigen presentation.
	Lipid-based nanoparticles	Controlled release and enhanced immune activation.
	Quantum dots	Fluorescence for tracking with immune stimulation.
Ovarian Cancer	Silica nanoparticles	Stability and antigen delivery.
	Liposomal nanoparticles	Enhanced antigen encapsulation and adjuvant properties.
	PLGA nanoparticles	Biocompatible and controlled release of antigens.
Liver Cancer	Iron oxide nanoparticles	Magnetic targeting and immune activation.
	Gold nanoparticles	Enhanced immune system activation and stability.
	Carbon nanotubes	High surface area for antigen delivery and strong immune response.
Cervical Cancer	Nanoliposomes	Effective antigen encapsulation and enhanced immune response.
	Polymeric nanoparticles	Controlled release and low toxicity.
	Gold nanoparticles	Increased immune activation and precise targeting.
	Quantum dots	Tracking capability with immune system activation.

Leukemia	Dendrimers	High surface area for multiple antigen loading and immune response.
	PLGA nanoparticles	Biodegradable with sustained antigen release.
Renal Cancer	Lipid-based nanoparticles	Enhanced delivery of antigens and immune activation.
	Chitosan nanoparticles	Biocompatibility and enhanced adjuvant effect.
	Gold nanoparticles	Strong adjuvant activity with immune targeting.
Brain Cancer	Polymeric nanoparticles (PLGA)	Ability to cross the blood-brain barrier and controlled antigen delivery.
	Silica nanoparticles	High stability and antigen presentation in biological systems.
	Lipid-based nanoparticles	Enhanced immune response and targeting.

5. Future challenges

In developing nanoadjuvants for cancer vaccines, one of the most critical challenges is the inherent complexities involved in the formulation of nanoparticles and the precise control of their size, shape, and surface area, which is one of the most critical challenges. As a result of these characteristics, nanoadjuvants are directly influenced by efficacy and safety, and mass production of these products at a large-scale poses a challenge when it comes to their production. Furthermore, when it comes to the production process and the precise characterization of nanoadjuvants, they must be designed to meet stability and reproducibility specifications (49). It is essential to recognize that this can be impacted by technological limitations in many cases. Similarly, nanoparticles can have non-uniform sizes or surfaces, resulting in a drastic change in their performance and a possible escalation of side effects if these are not addressed. Developing nanoadjuvants is one of the most significant challenges scientists face due to safety concerns. Even though many preclinical studies have demonstrated that nanoparticles can benefit human health, concerns remain regarding their long-term toxicity to the human body after intake (50). Depending

on which nanoparticles are ingested, they may accumulate in the body and cause inflammation and damage to vital tissues such as the liver, the kidneys, or the lungs. Studies over a long period are required to evaluate nanoadjuvant adverse effects accurately. Furthermore, it is imperative to stress that the differences between the human immune system and those used in animal models make it difficult to generalize preclinical results to humans. This highlights the need for extensive clinical trials.

It is also important to note that the high cost of production and the lack of commercialization of nanoadjuvant technology is one of the challenges to developing nanoadjuvants. Nanoparticle production involves advanced technologies and expensive raw materials. This can impede the introduction of these products to a broad market because of technological barriers. Additionally, these difficulties are exacerbated by the costs associated with clinical research and regulatory agencies. As a result of improved efficacy and reduced need for more expensive treatment methods, if nanoadjuvants prove to be effective in clinical trials, there will be a decrease in the cost of cancer vaccines because more effective treatments can be used, thereby reducing treatment costs. Furthermore, nanoadjuvant development has been hindered by several regulatory issues and problems associated with approvals and regulations. Nanoadjuvants have yet to be approved by many regulatory bodies, including the United States Food and Drug Administration (FDA), which approves drugs and pharmaceuticals. Considering the complexity associated with evaluating nanoparticle safety and effectiveness, adhering to the current regulatory requirements may not be feasible based on the currently used criteria. To facilitate the approval and entry process of these technologies into the market as fast and efficiently as possible, it is essential to develop new and integrated guidelines for evaluating nanoadjuvants as soon as possible.

Moreover, nanoadjuvants are expected to focus on improving nanoparticle design and manufacturing to be safer and more effective. This will be done using new combinations of nanomaterials and combining nanoadjuvants with other immunotherapy approaches. This will further improve nanoadjuvant efficacy and safety. Currently, researchers are designing nanoparticles capable of enhancing the immune response, possessing the fewest side effects, and targeting cancer cells only. In this regard, technologies like nanoparticles coated with targeted ligands or antibodies may penetrate tumors more effectively. The immune system may generate more precise responses. In addition to recent advances in bioinformatics and computer modeling, recent advances in nanotechnology have opened up new possibilities for designing and evaluating nanoadjuvants. Using these technologies, researchers can simulate nanoadjuvant performance and safety and predict their performance and safety before conducting experiments. This is to determine if they perform as expected. Significant reductions in nanoparticle development costs have been achieved due to this method, and the design process can be accelerated. Furthermore, computational models can also help assess possible risks and side effects of nanoadjuvants faster and more accurately.

In the future, there is a possibility of integrating nanoadjuvants with other new technologies, such as gene editing and immunotherapy using chimeric antigen receptor (CAR) CAR-T cells, within a nanoadjuvant combination. This could treat cancer. By combining these two approaches, a more remarkable ability to enhance personalized immune responses can be achieved, as well as better therapeutic outcomes. It has been shown that nanoadjuvants can work in conjunction with modified T cells to enhance the effectiveness of cell therapies. This is done by reducing tumor immune inhibition and acting as immunoenhancing agents. Using such strategies, it might be possible to introduce more efficient and accurate treatments for cancer that are more targeted and

precise. Developing nanoadjuvants and commercializing these products is essential to establish interdisciplinary collaborations and partnerships across universities, pharmaceutical companies, and regulatory bodies. This is to achieve success. Developing efficient and safe nanoadjuvants requires a comprehensive and coordinated approach. This combines basic, preclinical, and clinical research and creates a coherent legal framework to ensure their safety. Additionally, raising financial investment levels and paying attention to production quality standards can help speed up the entry of these technologies into the market to improve treatment results for cancer patients (Table 2) (Figure 2).

Table 2. This table provides a broad overview of the challenges, related cancer types, and potential solutions in nanovaccines.

Type of Cancer	Challenge	Solution
Lung Cancer	Poor immune response	Enhance adjuvant properties using nanoparticle delivery systems.
Breast Cancer	Limited targeting specificity	Utilize targeted ligands or antibodies on nanoparticles for specific tumor targeting.
Liver Cancer	Nanoparticle toxicity	Use biodegradable and biocompatible materials for nanoparticle formulation.
Pancreatic Cancer	Short circulation time	Modify nanoparticles with PEGylation to improve circulation and stability.
Ovarian Cancer	High production costs	Optimize scalable and cost-effective manufacturing processes.
Colorectal Cancer	Lack of long-term clinical data	Conduct extensive long-term clinical trials to evaluate efficacy and safety.
Melanoma	Immune suppression in tumor microenvironment	Combine nanovaccines with immune checkpoint inhibitors to counteract immunosuppression.
Prostate Cancer	Poor patient compliance	Develop oral or less invasive vaccine delivery methods for ease of administration.
Brain Cancer	Difficulty in crossing biological barriers	Design nanoparticles with enhanced permeability for crossing the blood-brain barrier (BBB).

Renal Cancer	Rapid clearance by the immune system	Use stealth nanoparticles that evade immune detection, such as through surface modifications.
Cervical Cancer	Resistance to treatment	Employ combination therapies that integrate nanovaccines with traditional treatments.
Leukemia	Heterogeneity of tumor cells	Use personalized nanovaccines based on patient-specific tumor antigens.

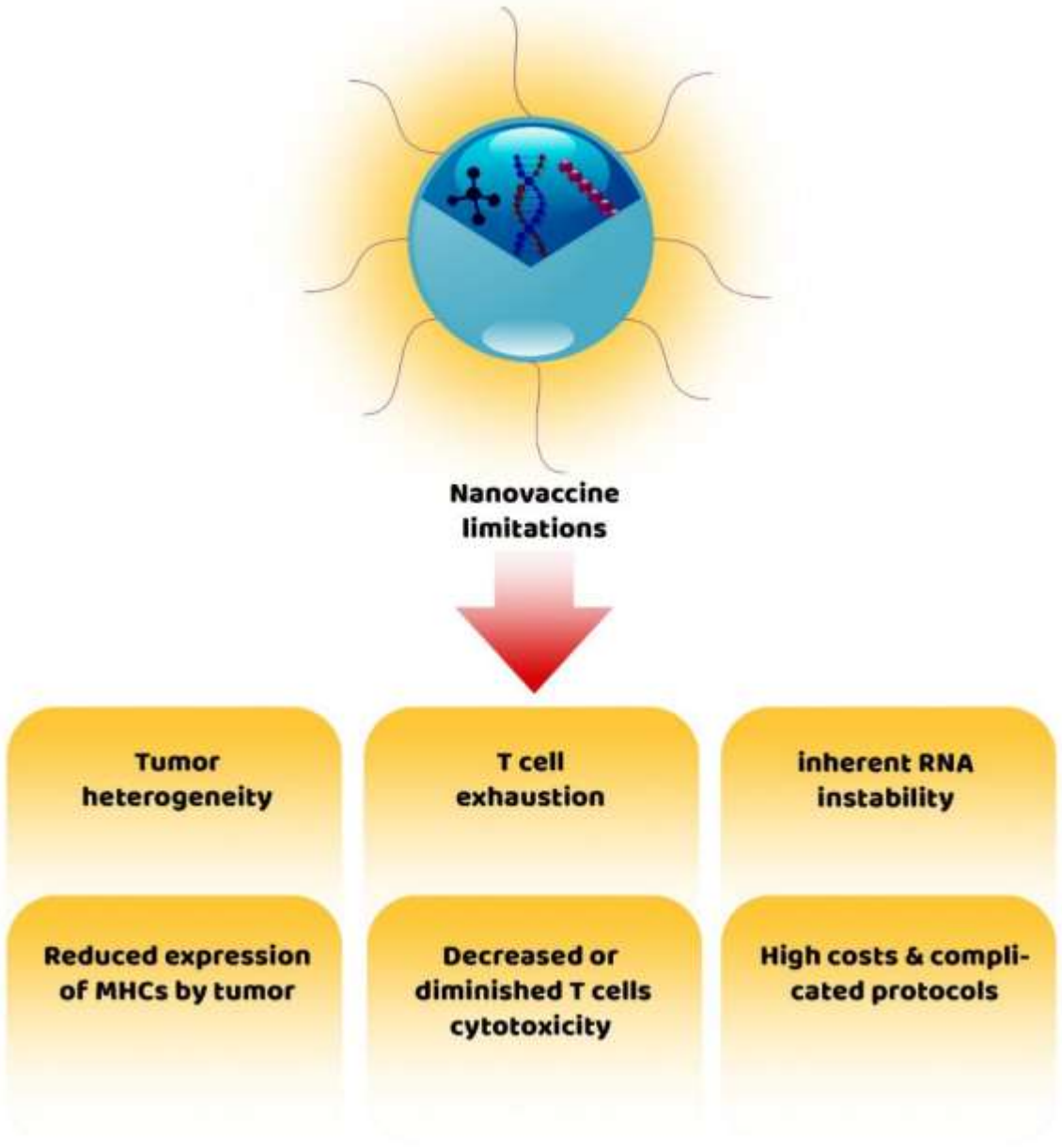

Figure 2. Challenges and limitations of cancer treatment with nanovaccines (36).

Conclusion

With the advent of nanoadjuvants, the development of cancer vaccines has made a tremendous leap forward, with promising potential to overcome some of the present limitations of immunotherapy. As nanoadjuvants enhance vaccine antigen presentation, stimulating dendritic cells and modulating innate and adaptive immune responses. This improves the efficacy of cancer vaccines. There is considerable evidence that these treatments improve immune responses and provide protection that lasts for a long time. Despite this, numerous challenges are connected to their safety, manufacturing in large quantities, and regulatory approvals. In conclusion, nanoadjuvants may play an essential role in developing next-generation cancer vaccines, which could lead to improved patient outcomes and cancer immune therapies.

Declarations and statements

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Author contribution

Conceptualization: [S.D.], …; Methodology: [S.A.A., S.E., N.M.], …; Formal analysis and investigation: [M.H., N.M., E.D.N.], …; Writing - original draft preparation: [M.H., N.M., E.D.N., N.H.S., M.F., F.Z., A.D.D., S.D.]; Writing - review and editing: [M.H., N.M., E.D.N., N.H.S., M.F., F.Z., A.D.D., S.D.], …; Funding acquisition: [Self-funding], …; Supervision: [S.D.]. All authors checked and approved the final version of the manuscript for publication in the present journal.

Ethical approval

On behalf of all co-authors, I hereby confirm that I have reviewed and complied with the relevant Instructions to Authors, the Ethics in Publishing policy, and Conflicts of Interest disclosure.

Conflict of interests

The authors declare no conflict of interest.

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Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Consent to participate:

Not applicable

Consent for publication:

Not applicable

References

1. Feng C, Li Y, Ferdows BE, Patel DN, Ouyang J, Tang Z, et al. Emerging vaccine nanotechnology: from defense against infection to sniping cancer. Acta Pharmaceutica Sinica B. 2022;12(5):2206-23. https://doi.org/10.1016/j.apsb.2021.12.021

2. Hosseini AM, Dianaty S, Shahhosseini S, Biglarifard R, Razmi R, Komeili N, et al. Advances in Nanotechnology for Enhanced Leukemia Therapy: A Systematic Review of In Vivo Studies. Journal of Lab Animal Research. 2023;2(6):86-99. https://doi.org/10.58803/jlar.v2i6.34

3. Soleymani N, Sadr S, Santucciu C, Dianaty S, Lotfalizadeh N, Hajjafari A, et al. Unveiling Novel Insights in Helminth Proteomics: Advancements, Applications, and Implications for Parasitology and Beyond. Biologics. 2024;4(3):314-44. https://doi.org/10.3390/biologics4030020

4. Xie X, Song T, Feng Y, Zhang H, Yang G, Wu C, et al. Nanotechnology-based multifunctional vaccines for cancer immunotherapy. Chemical Engineering Journal. 2022;437:135505. https://doi.org/10.1016/j.cej.2022.135505

5. He R, Zang J, Zhao Y, Dong H, Li Y. Nanotechnology-based approaches to promote lymph node targeted delivery of cancer vaccines. ACS Biomaterials Science & Engineering. 2022;8(2):406-23. https://doi.org/10.1021/acsbiomaterials.1c01274

6. Guo J, Tang L, Li K, Ma Q, Luo S, Cheng R, et al. Application of nanotechnology in therapeutic cancer vaccines. Advanced NanoBiomed Research. 2023;3(7):2200122. https://doi.org/10.1002/anbr.202200122

7. Kemp JA, Kwon YJ. Cancer nanotechnology: current status and perspectives. Nano convergence. 2021;8(1):34. https://doi.org/10.1186/s40580-021-00282-7

8. Zhou J, Kroll AV, Holay M, Fang RH, Zhang L. Biomimetic nanotechnology toward personalized vaccines. Advanced materials. 2020;32(13):1901255. https://doi.org/10.1002/adma.201901255

9. Hajjafari A, Sadr S, Rahdar A, Bayat M, Lotfalizadeh N, Dianaty S, et al. Exploring the integration of nanotechnology in the development and application of biosensors for enhanced detection and monitoring of colorectal cancer. Inorganic Chemistry Communications. 2024:112409. https://doi.org/10.1016/j.inoche.2024.112409

10. Bockamp E, Rosigkeit S, Siegl D, Schuppan D. Nano-enhanced cancer immunotherapy: immunology encounters nanotechnology. Cells. 2020;9(9):2102. https://doi.org/10.3390/cells9092102

11. Ren H, Jia W, Xie Y, Yu M, Chen Y. Adjuvant physiochemistry and advanced nanotechnology for vaccine development. Chemical Society Reviews. 2023;52(15):5172-254. https://doi.org/10.1039/D2CS00848C

12. Liu G, Zhu M, Zhao X, Nie G. Nanotechnology-empowered vaccine delivery for enhancing CD8+ T cells-mediated cellular immunity. Advanced drug delivery reviews. 2021;176:113889. https://doi.org/10.1016/j.addr.2021.113889

13. Akkın S, Varan G, Bilensoy E. A review on cancer immunotherapy and applications of nanotechnology to chemoimmunotherapy of different cancers. Molecules. 2021;26(11):3382. https://doi.org/10.3390/molecules26113382

14. Chen Y. Nanotechnology for next-generation cancer immunotherapy: State of the art and future perspectives. Journal of Controlled Release. 2023;356:14-25. https://doi.org/10.1016/j.jconrel.2023.02.016

15. Gao S, Yang X, Xu J, Qiu N, Zhai G. Nanotechnology for boosting cancer immunotherapy and remodeling tumor microenvironment: the horizons in cancer treatment. ACS nano. 2021;15(8):12567-603. https://doi.org/10.1021/acsnano.1c02103

16. Chauhan DS, Dhasmana A, Laskar P, Prasad R, Jain NK, Srivastava R, et al. Nanotechnology synergized immunoengineering for cancer. European journal of pharmaceutics and biopharmaceutics. 2021;163:72-101. https://doi.org/10.1016/j.ejpb.2021.03.010

17. Chen S, Huang X, Xue Y, Álvarez-Benedicto E, Shi Y, Chen W, et al. Nanotechnology-based mRNA vaccines. Nature Reviews Methods Primers. 2023;3(1):63. https://doi.org/10.1038/s43586-023-00246-7

18. Zhao Y, Bilal M, Qindeel M, Khan MI, Dhama K, Iqbal HM. Nanotechnology-based immunotherapies to combat cancer metastasis. Molecular Biology Reports. 2021;48(9):6563-80. https://doi.org/10.1007/s11033-021-06660-y

19. Koyande NP, Srivastava R, Padmakumar A, Rengan AK. Advances in nanotechnology for cancer immunoprevention and immunotherapy: a review. Vaccines. 2022;10(10):1727. https://doi.org/10.3390/vaccines10101727

20. Davodabadi F, Sarhadi M, Arabpour J, Sargazi S, Rahdar A, Díez-Pascual AM. Breast cancer vaccines: New insights into immunomodulatory and nano-therapeutic approaches. Journal of Controlled Release. 2022;349:844-75. https://doi.org/10.1016/j.jconrel.2022.07.036

21. Lin Y-X, Wang Y, Blake S, Yu M, Mei L, Wang H, et al. RNA nanotechnology-mediated cancer immunotherapy. Theranostics. 2020;10(1):281. https://doi.org/10.7150/thno.35568

22. Zhou X, Lian H, Li H, Fan M, Xu W, Jin Y. Nanotechnology in cervical cancer immunotherapy: Therapeutic vaccines and adoptive cell therapy. Frontiers in Pharmacology. 2022;13:1065793. https://doi.org/10.3389/fphar.2022.1065793

23. Li Y, Miao W, He D, Wang S, Lou J, Jiang Y, et al. Recent progress on immunotherapy for breast cancer: tumor microenvironment, nanotechnology and more. Frontiers in Bioengineering and Biotechnology. 2021;9:680315. https://doi.org/10.3389/fbioe.2021.680315

24. Zhang H, Xia X. RNA cancer vaccines: developing mRNA nanovaccine with self-adjuvant property for cancer immunotherapy. Human Vaccines & Immunotherapeutics. 2021;17(9):2995-8. https://doi.org/10.1080/21645515.2021.1921524

25. Assis BRD, da Silva CD, Santiago MG, Ferreira LAM, Goulart GAC. Nanotechnology in adjuvants and vaccine development: what should we know? : Taylor & Francis; 2021. p. 2565-8. https://doi.org/10.2217/nnm-2021-0360

26. Feng C, Tan P, Nie G, Zhu M, editors. Biomimetic and bioinspired nano- platforms for cancer vaccine development. Exploration; 2023: Wiley Online Library. https://doi.org/10.1002/EXP.20210263

27. Ahmad MZ, Ahmad J, Haque A, Alasmary MY, Abdel-Wahab BA, Akhter S. Emerging advances in synthetic cancer nano-vaccines: opportunities and challenges. Expert review of vaccines. 2020;19(11):1053-71. https://doi.org/10.1080/14760584.2020.1858058

28. Liu J, Miao L, Sui J, Hao Y, Huang G. Nanoparticle cancer vaccines: Design considerations and recent advances. Asian Journal of Pharmaceutical Sciences. 2020;15(5):576-90. https://doi.org/10.1016/j.ajps.2019.10.006

29. Beg S, Alharbi KS, Alruwaili NK, Alotaibi NH, Almalki WH, Alenezi SK, et al. Nanotherapeutic systems for delivering cancer vaccines: recent advances. Nanomedicine. 2020;15(15):1527-37. https://doi.org/10.2217/nnm-2020-0046

30. Qian C, Yang L-J, Cui H. Recent advances in nanotechnology for dendritic cell-based immunotherapy. Frontiers in Pharmacology. 2020;11:960. https://doi.org/10.3389/fphar.2020.00960

31. Chatzikleanthous D, Schmidt ST, Buffi G, Paciello I, Cunliffe R, Carboni F, et al. Design of a novel vaccine nanotechnology-based delivery system comprising CpGODN-protein conjugate anchored to liposomes. Journal of Controlled Release. 2020;323:125-37. https://doi.org/10.1016/j.jconrel.2020.04.001

32. Goradel NH, Nemati M, Bakhshandeh A, Arashkia A, Negahdari B. Nanovaccines for cancer immunotherapy: Focusing on complex formation between adjuvant and antigen. International Immunopharmacology. 2023;117:109887. https://doi.org/10.1016/j.intimp.2023.109887

33. Aikins ME, Xu C, Moon JJ. Engineered nanoparticles for cancer vaccination and immunotherapy. Accounts of chemical research. 2020;53(10):2094-105. https://doi.org/10.1021/acs.accounts.0c00456

34. Zeng H, Li J, Hou K, Wu Y, Chen H, Ning Z. Melanoma and nanotechnology-based treatment. Frontiers in oncology. 2022;12:858185. https://doi.org/10.3389/fonc.2022.858185

35. Wu Y, Zhang Z, Wei Y, Qian Z, Wei X. Nanovaccines for cancer immunotherapy: current knowledge and future perspectives. Chinese Chemical Letters. 2023;34(8):108098. https://doi.org/10.1016/j.cclet.2022.108098

36. Fang X, Lan H, Jin K, Gong D, Qian J. Nanovaccines for cancer prevention and immunotherapy: an update review. Cancers. 2022;14(16):3842. https://doi.org/10.3390/cancers14163842

37. Peres C, Matos AI, Moura LI, Acurcio RC, Carreira B, Pozzi S, et al. Preclinical models and technologies to advance nanovaccine development. Advanced Drug Delivery Reviews. 2021;172:148-82. https://doi.org/10.1016/j.addr.2021.03.001

38. Fontana F, Figueiredo P, Santos HA. Advanced nanovaccines for immunotherapy applications: From concept to animal tests. Theranostic bionanomaterials: Elsevier; 2019. p. 231-60. https://doi.org/10.1016/B978-0-12-815341-3.00010-9

39. Liao Z, Huang J, Lo P-C, Lovell JF, Jin H, Yang K. Self-adjuvanting cancer nanovaccines. Journal of Nanobiotechnology. 2022;20(1):345. https://doi.org/10.1186/s12951-022-01545-z

40. Terán-Navarro H, Calderon-Gonzalez R, Salcines-Cuevas D, García I, Marradi M, Freire J, et al. Pre-clinical development of Listeria-based nanovaccines as immunotherapies for solid tumours: insights from melanoma. Oncoimmunology. 2019;8(2):e1541534. https://doi.org/10.1080/2162402X.2018.1541534

41. Kang T, Huang Y, Zhu Q, Cheng H, Pei Y, Feng J, et al. Necroptotic cancer cells-mimicry nanovaccine boosts anti-tumor immunity with tailored immune-stimulatory modality. Biomaterials. 2018;164:80-97. https://doi.org/10.1016/j.biomaterials.2018.02.033

42. Gurunathan S, Thangaraj P, Wang L, Cao Q, Kim J-H. Nanovaccines: an effective therapeutic approach for cancer therapy. Biomedicine & Pharmacotherapy. 2024;170:115992. https://doi.org/10.1016/j.biopha.2023.115992

43. Xia J, Miao Y, Wang X, Huang X, Dai J. Recent progress of dendritic cell-derived exosomes (Dex) as an anti-cancer nanovaccine. Biomedicine & Pharmacotherapy. 2022;152:113250. https://doi.org/10.1016/j.biopha.2022.113250

44. Zhang L, Zhao W, Huang J, Li F, Sheng J, Song H, et al. Development of a dendritic cell/tumor cell fusion cell membrane nano-vaccine for the treatment of ovarian cancer. Frontiers in immunology. 2022;13:828263. https://doi.org/10.3389/fimmu.2022.828263

45. Mohsen MO, Vogel M, Riether C, Muller J, Salatino S, Ternette N, et al. Targeting mutated plus germline epitopes confers pre-clinical efficacy of an instantly formulated cancer nano-vaccine. Frontiers in immunology. 2019;10:1015. https://doi.org/10.3389/fimmu.2019.01015

46. Qin L, Zhang H, Zhou Y, Umeshappa CS, Gao H. Nanovaccine- based strategies to overcome challenges in the whole vaccination cascade for tumor immunotherapy. Small. 2021;17(28):2006000. https://doi.org/10.1002/smll.202006000

47. Zhang J, Fan J, Skwarczynski M, Stephenson RJ, Toth I, Hussein WM. Peptide-based nanovaccines in the treatment of cervical cancer: a review of recent advances. International Journal of Nanomedicine. 2022:869-900. https://doi.org/10.2147/IJN.S269986

48. Mamuti M, Chen W, Jiang X. Nanotechnology- Assisted Immunoengineering for Cancer Vaccines. Advanced NanoBiomed Research. 2023;3(1):2200080. https://doi.org/10.1002/anbr.202200080

49. Chen K, Wu Z, Zang M, Wang C, Wang Y, Wang D, et al. Immunization with glypican-3 nanovaccine containing TLR7 agonist prevents the development of carcinogen-induced precancerous hepatic lesions to cancer in a murine model. American journal of translational research. 2018;10(6):1736.

50. Meng Z, Zhang Y, Zhou X, Ji J, Liu Z. Nanovaccines with cell-derived components for cancer immunotherapy. Advanced drug delivery reviews. 2022;182:114107. https://doi.org/10.1016/j.addr.2021.114107