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Review Article

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 activating 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 due to 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 possess 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 duration and specificity of the immune response over an extended period. Moreover, the review discusses the potential application of nanoadjuvants in highly customized cancer vaccines, in which the nanoformulation is 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

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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. In conclusion, this review provides an overview of the future directions of nanoadjuvants in cancer immunotherapy and emphasizes the need for interdisciplinary collaborative efforts to address existing challenges and fully unlock the potential of this innovative approach.

1. Context

A vaccine is widely recognized as one of the most effective ways to prevent and treat disease, and it 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 it, with immunotherapy employed as one of the most effective techniques [2, 3]. Vaccines against cancer serve to stimulate the body's immune system to recognize and destroy cancer cells when they are injected [4]. While infectious disease vaccines, which have achieved wide dissemination over the past few decades, often face obstacles such as the lack of a robust and sustained immune response, cancer vaccines have not been as successful [5]. In most cases, these problems are caused by cancer antigens, which cannot generate strong immune responses and therefore fail to stimulate the immune system effectively [6]. Cancer cells are naturally recognized and destroyed by the body's immune system as soon as they become abnormal. Despite this, cancer cells may escape immune detection because they closely resemble normal, non–cancerous cells [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 conducted 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 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 created a 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 areas of the body. 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 their 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 (DCs) [11]. DCs 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 adaptive 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 at 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 up these nanoadjuvants is another existing challenge.

Despite these challenges, nanoadjuvants are recognized as one of the most important new tools in developing cancer vaccines, and more research is being conducted 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 the 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 these cells [20]. In addition, DCs 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 antigen presentation. Nanoadjuvants activate DCs by presenting antigens to them so that they can recognize the antigen. DCs mature after absorbing nanoparticles and antigens and produce cytokines and stimulatory molecules, which stimulates 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 DCs and thus promoting T cell activation [23].

In addition to directly stimulating DCs and T cells, nanoadjuvants also induce innate immune responses. Nanoparticles activate innate immune system signaling pathways, leading to the production of interferons and inflammatory cytokines [24]. These cytokines are essential for strengthening adaptive 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 adaptive 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 the 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 alter the microcellular environment of tumors, making it more suitable for immune system activity [30]. In many tumors, the microcellular environment is immunosuppressive, preventing immune cells from penetrating and destroying cancer cells. Nanoadjuvants can improve immune cell penetration and activity conditions by stimulating cytokine production and altering the cellular composition of 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 be considered 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 precisely to tumor or lymph node sites, maximizing cancer vaccine efficacy [35]. This fine-tuning results in fewer side effects and a stronger, more stable immune response (Figure 1).

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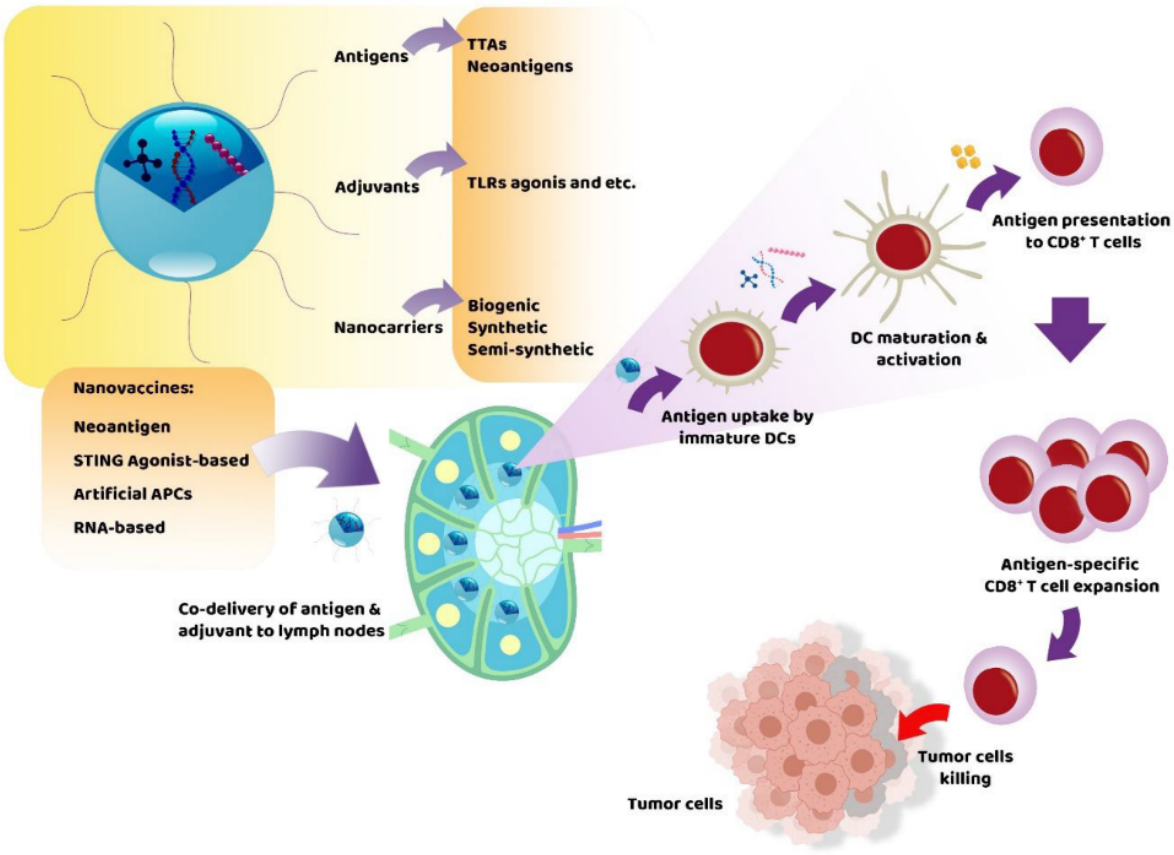

Figure 1. Nanovaccines in the treatment of cancer [36]

Abbreviations: APC: Antigen-presenting cell; DC: Dendritic cell; TAAs: Tumor-associated antigens; TLR: Toll-like receptor.

Note: The general structure of nanovaccines, their types, and the mechanism of action of this type of vaccine are shown. After the administration of a nanovaccine and the delivery of antigens and adjuvants to lymphoid tissues, antigens are taken up by DCs, resulting in DC maturation and activation. After this stage, matured DCs present the antigens toe CD8+ T cells through major histocompatibility complex molecules, causing T cell expansion. Finally, antigen-specific T cells invade and kill tumor cells in the tumor microenvironment.

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 the immunogenic effects of nanoadjuvant on living organisms during complex research. Several animal models have been developed, such as lab mice, which 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 immune system. It is possible to determine how nanoparticles are transported, how DCs absorb them, and whether it is possible to enhance immune 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, which are among 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 alter 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 primate 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 is important 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 or monkeys, can provide more accurate results because their immune systems are more similar to humans than those of smaller animals. Even though they are more complex and expensive, they are also more suitable. Several recent preclinical studies on mouse 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 was a study 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 stable immune memory, which prevented the tumor from regrowing in the long run. Based on these results, nanoadjuvants can produce lasting immunity against 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 cellular 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. Transplanted tumor models are more widely used due to their ease of establishment and faster reaction control. Still, induced 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 foundation 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. Confirmation of these findings in human experimental studies is essential. Such an approach can ensure the successful transfer of nanoadjuvants to clinical applications (Table 1).

5. Future Challenges

In developing nanoadjuvants for cancer vaccines, one of the most critical challenges is the inherent complexity involved in the formulation of nanoparticles and the precise control of their size, shape, and surface area. As a result of these characteristics, nanoadjuvant efficacy and safety are directly influenced, and mass production of these products at a large scale poses a challenge. 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 certain 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 issues 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, kidneys, or lungs. Studies over a long period are required to accurately evaluate nanoadjuvant adverse effects. Furthermore, it is imperative to stress that the differences between the human immune system and those of animal models make it difficult to generalize preclinical results to humans. This highlights the need for extensive clinical trials.

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Table 1. An review of 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.
	Poly(lactic-co-glycolic) acid (PLGA) nanoparticles	Biodegradable and controlled antigen release.
Breast cancer	Gold nanoparticles	Enhanced targeting and immune activation.
	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.
Leukemia	Quantum dots	Tracking capability with immune system activation.
	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 BBB and controlled antigen delivery.
	Silica nanoparticles	High stability and antigen presentation in biological systems.
	Lipid-based nanoparticles	Enhanced immune response and targeting.

Table 2. An overview of the challenges, related cancer types, and potential solutions in nanovaccine development

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.

It is also important to note that the high cost of production and the lack of commercialization of nanoadjuvant technology are among 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. If nanoadjuvants prove to be effective in clinical trials, their improved efficacy and reduced need for more expensive treatment methods could lead to a decrease in the cost of cancer vaccines, thereby reducing overall treatment costs. Furthermore, nanoadjuvant development has been hindered by several regulatory issues and challenges associated with approvals. Nanoadjuvants have yet to be approved by many regulatory bodies, including the United States Food and Drug Administration (FDA), which oversees the approval of drugs and pharmaceuticals. Considering the complexity associated with evaluating nanoparticle safety and effectiveness, adhering to current regulatory requirements may not be feasible based on existing criteria. To facilitate the approval and market entry of these technologies as quickly and efficiently as possible, it is essential to develop new and integrated guidelines for evaluating nanoadjuvants.

Moreover, future development of nanoadjuvants is expected to focus on improving nanoparticle design and manufacturing to enhance safety and effectiveness. This will be done using new combinations of nanomaterials and by 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 minimal side effects, and targeting cancer cells specifically. 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, 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 behavior before conducting experiments. This helps determine whether they perform as expected. Significant reductions in nanoparticle development costs have been achieved through this method, and the design process can be accelerated. Furthermore, computational models can help assess possible risks and side effects of nanoadjuvants more quickly and 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) T cells, within a nanoadjuvant combination. This could help treat cancer. By combining these approaches, a greater ability to enhance personalized immune responses and achieve better therapeutic outcomes can be realized. It has been shown that nanoadjuvants can work in conjunction with modified T cells to enhance the ef-

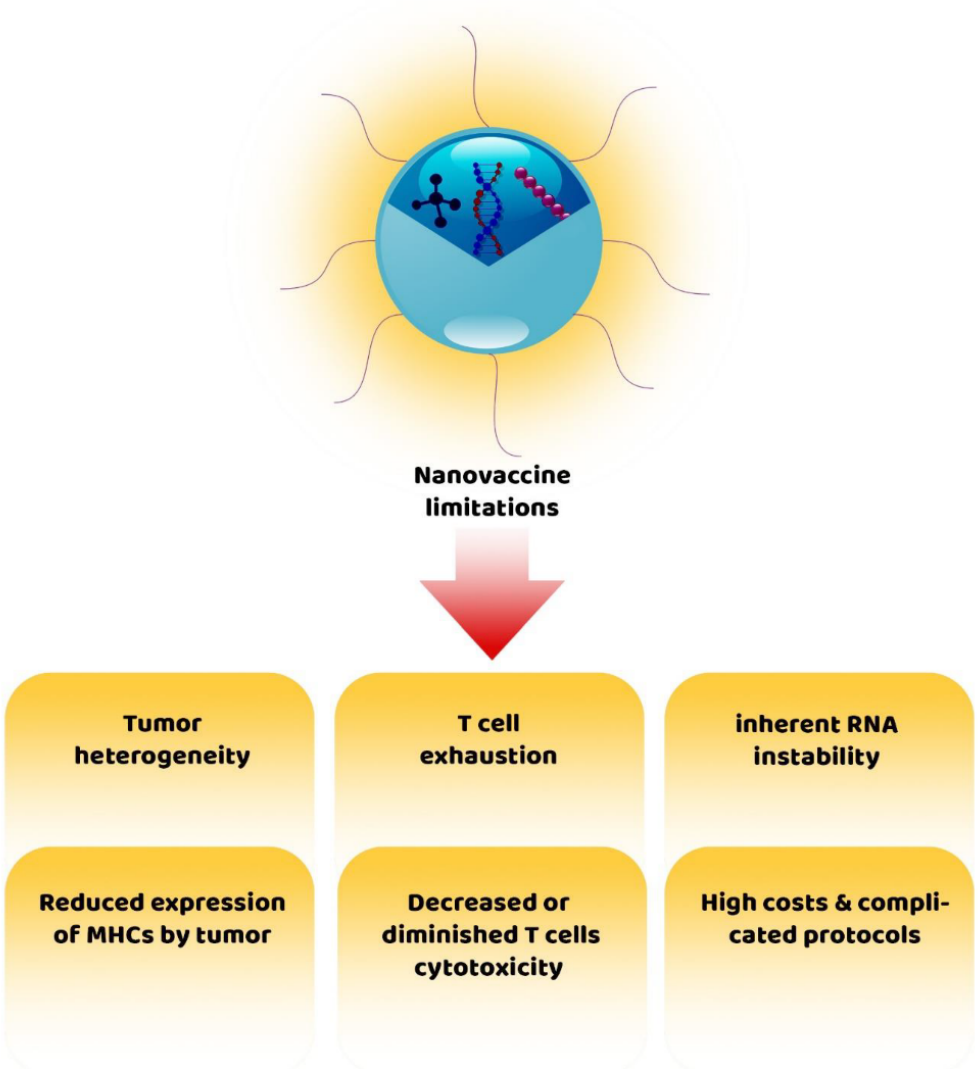

Figure 2. Challenges and limitations of cancer treatment using nanovaccines [36]

fectiveness of cell therapies. This is achieved by reducing tumor immune inhibition and acting as immunoenhancing agents. Using such strategies, it might be possible to introduce more efficient and accurate cancer treatments that are more targeted and precise. Developing nanoadjuvants and commercializing these products is essential for establishing interdisciplinary collaborations and partnerships across universities, pharmaceutical companies, and regulatory bodies. Developing efficient and safe nanoadjuvants requires a comprehensive and coordinated approach. This combines basic, preclinical, and clinical research and helps create a coherent legal framework to ensure their safety. Additionally, increasing financial investment and focusing on production quality standards can help accelerate the entry of these technologies into the market and improve treatment outcomes for cancer patients (Table 2, Figure 2).

6. 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. Nanoadjuvants enhance vaccine antigen presentation, stimulate DCs, and modulate innate and adaptive immune responses. This improves the efficacy of cancer vaccines. There is considerable evidence that these treatments improve immune responses and provide long-lasting protection. Despite this, numerous challenges remain related to their safety, large-scale manufacturing, and regulatory approvals. In conclusion, nanoadjuvants may play an essential role in developing next-generation cancer vaccines, potentially leading to improved patient outcomes and more effective cancer immunotherapies.

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Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

Data availability

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

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Authors' contributions

Supervision: Shiva Dianaty; All authors contributed equally to the conception and design of the study, data collection and analysis, interception of the results and drafting of the manuscript. Each author approved the final version of the manuscript for submission.

Conflict of interest

The authors declared no conflict of interest.

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