

Nanobiotechnology-Enabled Smart Delivery Platforms for Targeted Cancer Immunotherapy: Recent Advances, Challenges, and Future Perspectives

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Article Info	ABSTRACT
<p>Article history:</p> <p>Received : 08.10.2025 Revised : 15.11.2025 Accepted : 20.12.2025</p>	<p>Immunotherapy of cancer has transformed oncology but still has limitations of low efficiency of delivery, off-target toxicity as well as resistance to therapy by the tumor microenvironment. Delivery systems that are conventional do not usually result in targeted, sustained, and immune-responsive release of therapeutics. The review underlines current developments in nanobiotechnology-enabled intelligent delivery systems such as lipid, polymeric, metallic, exosome-based, and DNA-origami systems, which can be used to improve the efficacy of cancer immunotherapy. The discussion summarizes the delivery mechanisms and immunological outcomes based on recent studies on the subject, with preclinical and clinical studies. There is evidence that demonstrates that smart nanocarriers enhance biodistribution, tumor targeting, immune checkpoint modulation, and reduce systemic toxicity. Taken together, these findings indicate that smart platforms based on nanobiotechnology have transformative potential in the next-generation precision immunotherapy, but their clinical implementation is limited.</p>
<p>Keywords:</p> <p>Nanobiotechnology, Smart delivery platforms, Cancer immunotherapy, Nanocarriers, Immune checkpoint blockade, Tumor microenvironment, Targeted drug delivery, Clinical translation</p>	

1. INTRODUCTION

The development of cancer immunotherapy has become one of the biggest achievements in the history of contemporary oncology providing a glimmer of hope against the incurable in the past cancer countries. Such therapeutic strategies as immune checkpoint inhibitors, cancer vaccines, chimeric antigen receptor (CAR)-T cell therapies have shown the capability to harness and manipulate the immune system of the body in order to selectively target the tumor cells. These discoveries have not only enhanced the existence of some cancers but have also changed the scene of dealing with cancer, which was at the time focused on destroying tumors directly to long-run disease control by using the immune system. Irrespective of these achievements, there still remain large shortcomings that impede the extensive effectiveness of immunotherapy. Although less effective in all groups of patients, when immune checkpoint inhibitors are administered, they result in severe immune-related adverse events caused by systemic immune stimulation. The cancer

vaccines usually face the difficulty of low antigen expression and direct removal during the circulation leading to a reduced potential to induce a sustained immune response. On the same note, short persistence in vivo, poor tumortumor trafficking, and immunosuppressive microenvironment are some of the barriers to CAR-T therapies. On a more global scale, systemic toxicity, low half-life of treatment modalities, tumor immunosuppressive mechanisms and the complexity of cancer biology are all underpinnings of the occurrence of different clinical responses. Nanobiotechnology has been found as an effective approach that can help to conquer these difficulties through offering novel delivery modalities that enhance the effectiveness, accuracy and safety of cancer immunotherapy. With the help of the special physicochemical characteristics of nanoscale structures, one can develop carriers that ensure the protection of therapeutic payload, increase their circulatory time and provide passive and active tumor targeting. Moreover, nanocarriers may also be programmed to react to

stimuli in the tumor microenvironment, and this method allows the local and targeted release of drugs, and reduces systemic side effects. In addition to the delivery, nanobiotechnology also enables the co-delivery of more than one therapeutic agent, including antigens and adjuvants in vaccinations or checkpoint inhibitors with immunostimulatory molecules and thus increases synergistic immune reactions.

This review is aimed at giving an overall account of the recent developments in the field of nanobiotechnology-based smart systems of delivery of targets to cancer immunotherapy. The focus is made on the various types of nanocarriers, their action mechanisms as well as the way they bypass the obstacles to successful immune modulation. Evidence provided by preclinical and clinical trials, determination of obstacles to clinical translation and prospects on the future of integrating nanotechnology with next-generation immunotherapy are also synthesized in the review. This paper will serve to highlight the transformative potential of nanobiotechnology by combining the disciplines of nanomedicine and oncology, and accordingly, it will be used to highlight how nanobiotechnology may change the future landscape of precise cancer therapy.

2. Nanobiotechnology in Cancer Immunotherapy

Nanobiotechnology is the combination of nanotechnology and biology systems in order to design, manipulate and use nanoscale materials to achieve therapeutic effects. In the field of oncology, it has become a paradigmatic change to improve the performance of immunotherapy by offering the most specialized delivery systems that can overcome the auto-inhibitory nature of traditional treatment techniques. It covers the creation of all the varied nanocarriers such as lipid-based nanoparticles, polymeric-based nanoparticles, inorganic nanostructures, and biomimetic platforms, each being customized to enhance the accuracy, stability and functionality of immune-targeted therapies [1], [2].

At the nanoscale, materials present peculiar physicochemical characteristics that may be used to enhance the process of delivery of drugs. Particle size is the determinant in biodistribution and tumor location with nanoparticles between 10 and 200nm having the potential to capitalise on the enhanced permeability and retention (EPR) effect to be passively accumulated in cancerous tissues [1], [4]. Surface charge has a high impact on circulation time, cellular uptake; electrostatic interactions of the positively charged carriers with the negatively charged cell membrane lead to an expansion of the blood circulation by the mononuclear phagocyte system, and neutral or

slightly negative surfaces also increase circulation time by reducing mononuclear phagocyte system clearance [3]. Additionally, active tumor-associated antigens or immune cell receptor recognition can occur because nanocarriers can be functionalized with targeting ligands, including antibodies, peptides or aptamers, which ensures high specificity of delivery [3], [4].

The benefits of nanobiotechnology in immunotherapy of cancer are not limited to tumour concentration and targeting. These systems allow the delivery of different therapeutic agents, including antigens in conjunction with adjuvants in vaccine preparations or checkpoint inhibitors with cytokines in combinations with each other, in a synergistic fashion to enhance immune activation [1], [4]. It is also possible to design smart nanocarriers that will react to intrinsic or extrinsic stimuli, such as pH, redox gradients, enzymes, or external fields, and allow controlled and localized drug delivery in the tumor microenvironment [5], [20]. Such designs are able not only to increase the therapeutic effect but also reduce adverse effects that are usually associated with systemic administration by minimizing systemic exposure and maximizing local effect. Altogether, nanobiotechnology is an advanced facilitator of targeted cancer immunotherapy due to the integration of the specificity of nanoscale engineering with the sophisticated process of immune modulation. Its ability to enhance drug stability, targeting, and delivery of multimodal therapeutic capacity highlight its promise in terminating to define the next generation of oncological therapies [1], [3].

3. Smart Delivery Platforms

3.1 Lipid-Based Systems (liposomes, lipid nanoparticles, solid lipid nanoparticles)

Lipid based systems are some of the most clinically viable nanocarriers because they have intrinsic biocompatibility of their nature as well as their ability to absorb both hydrophobic and hydrophilic therapeutic agents. The use of liposomes to deliver anticancer drugs and immunomodulatory molecules has received significant attention, but lipid nanoparticles (LNPs) became known to everyone with the effectiveness of mRNA vaccines. They are now modified to cancer immunotherapy, especially in the creation of mRNA-based cancer-vaccines and enhanced delivery of immune checkpoint-inhibitors [6], [7]. Nanoparticles of solid lipids also expand this platform by offering higher stability conditions and regulation of FRS to permit them to be suitable to be taken as a long-term therapeutic action.

3.2 Polymeric Nanocarriers (PLGA, dendrimers, hydrogels)

Polymeric nanocarriers, such as poly (lactic-co-glycolic acid) (PLGA) nanoparticles, dendrimers, and hydrogels, have the advantage of being biodegradable and being syntizable to have controlled release kinetics. PLGA is suitable and used in cancer treatment because it is FDA-approved and used with sustained drug release [8]. Dendrimers, due to their highly branched and multi-valent structures, are also useful in surface functionalization with targeting ligands and in the co-delivery of multiple agents, which is why they are useful in immunotherapy [9]. Hydrogels, however, serve as local drug depots, which release cytokines, checkpoint inhibitors, or tumor antigens with a prolonged effect on the local immune activation [10].

3.3 Inorganic/Metallic Nanoparticles (gold, iron oxide, silica)

Inorganic and metallic nanoparticles have the advantageous property of being theranostic because they combine therapeutic with diagnostic properties. Specifically, nanoparticles of gold find their best use in areas of photothermal and photo-immunotherapy whereby the heat production is integrated with immune response [11]. Iron oxide nanoparticles are a safe clinical imaging medication approved that allows drug delivery and can also be used to perform magnetic resonance imaging (MRI)-guided therapy [12]. The mesoporous silica nanoparticles, with their large surface area and well-controllable pore architecture, have a broad cargo loading capacity to immunological cargos and can be stimuli-responsive upon release under the conditions in the tumor microenvironment [13].

3.4 Biomimetic Nanocarriers (exosomes, cell-membrane coated nanoparticles)

The exosomes and cell membrane-coated nanoparticles used as biomimetic systems are the future of smart delivery strategies. Engineered exosomes, which are naturally released, extracellular vesicles, are capable of transporting therapeutic cargos (siRNA, antigens, adjuvants) directly to immune cells [14], [19]. Equally, nanoparticles wrapped in cell membranes of leukocytes or cancer cells inherit surface proteins to avoid immune targeting and homotypic targeting. This will enhance tumor penetration and minimize recognition and clearance by the host immune system [15].

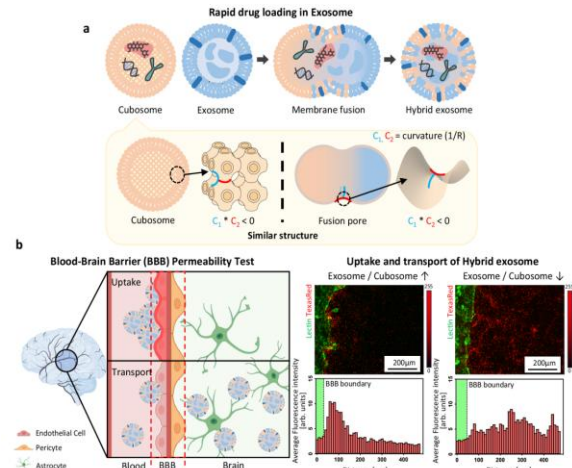


Fig. X: Development and evaluation of hybrid exosomes as smart nanobiotechnology-enabled delivery systems.

(a) Schematic and experimental workflow showing fusion of cubosomes with exosomes for rapid drug loading. (b) Blood-brain barrier (BBB) permeability test demonstrating uptake, transport, and distribution of hybrid exosomes compared to controls, highlighting their potential for targeted delivery in cancer immunotherapy.

3.5 Emerging Platforms (DNA origami, smart microrobots, stimuli-responsive carriers)

The future of nanobiotechnology in cancer immunotherapy is pointed out by the emergence of new systems of delivery. DNA origami nanostructures can provide programmable structures in which drugs can be encapsulated and released at a desired position [16]. Microrobots powered by magnetic forces or by biological forces are becoming possibilities to traverse complicated tumor environments and deliver drugs to tumor tissues [17]. Stimuli-responsive carriers respond in pH, enzymatic activity, redox potential or other external stimuli such as light and ultrasound to give spatially and temporally controlled drug delivery, reducing systemic side effects [18]. Together, these intelligent delivery systems can be described as an example of how nanobiotechnology is flexible and innovative in finding solutions to the cancer immunotherapy problem. Individual platforms add distinct functions which amplify the stability of drugs, efficacy of targeting and immune modulation leading to more effective and clinically translatable therapies.

4. Mechanisms of Targeted Cancer Immunotherapy Using Nanocarriers

The nanocarrier has been noted to become a potent facilitator of targeted cancer immunotherapy through enhancement of the

efficiency of drug delivery, target site release, as well as minimization of systemic toxicity. The design will enable therapeutic agents to bypass physiological barriers and be more involved in the immune system. A number of mechanisms explain the use of nanobiotechnology in immune modulation in cancer therapy. Nanocarriers can be used to promote many immunotherapy approaches on the mechanistic level, such as immunotherapy involving checkpoint blockade, tumor vaccinations, cytokine therapy, adoptive T cell therapies, and tumor microenvironment reprogramming (Figure 2).

One of the most effective performances of nanocarriers is immune checkpoint blockade delivery. The traditional method of administration of checkpoint inhibitors including Rivuloxab anti-PD-1, Rivuloxab anti-PD-L1 and anti-CTLA-4 antibodies is also linked with systemic immune activation and ruthless adverse autoimmune events. With the help of their encapsulation or conjugation to nanocarriers, it is possible to deliver these antibodies to the tumor site locally to maximize their therapeutic effect and reduce their off-target toxicity. Moreover, delivery by nanoparticles allows checkpoint inhibitor to be given in synergy with adjuvants or cytokine, thereby producing synergistic antigens.

Nanotechnology can also be useful when it comes to cancer vaccines by combining the delivery of antigens and adjuvants in a single system. Nanoparticles have the potential to prevent the untimely degradation of delicate antigens, increase antigen uptake by antigen presenting cells and sustain stable antigen expression by T cells. Lipid nanoparticles and polymeric carriers are especially useful in the delivery of mRNA and peptide vaccines, and thus, elicit enhanced cytotoxic T lymphocyte tumor-associated antigen responses.

Poor pharmacokinetics and systemic toxicity have been conventional restrictive factors in cytokine delivery. Nanocarriers provide the control and localization of the release of such cytokines as interleukin-2 (IL-2) and interleukin-15 (IL-15) that are crucial triggering T cell and natural killer (NK) cell activation. Nanoparticles stimulate immune responses in the tumor microenvironment which is the main strategy of cytokine release but has minimal side effects on other systemic processes.

Nanotechnology can further enhance CAR-T as well as adoptive cell therapy. Non-viral vectors Nanoparticles are under development as alternative methods of genetic transport in T cells than viral transduction, which is safer and scalable. Besides the delivery of genes, nanoparticles may be designed to deliver stimulatory molecules or cytokines directly to adoptively transferred cells in order to enhance their persistence, proliferation, and tumor infiltration. Such combination of

nanocarriers and cellular immunotherapy is likely to reduce weaknesses of CAR-T in solid tumors. Another important mechanism is the tumor microenvironment reprogramming. The microenvironment of tumor immunosuppression tends to inhibit the activity of immunotherapy through a decrease in the infiltration of T cells, an increase in the activity of suppressor cells, and a change in metabolism. Nanocarriers may be programmed to release oxygen, neutralize acidic environment or to deposit enzymes breaking down the matrix to remodel the stromal architecture. These interventions stabilise the microenvironment in the tumour, stimulate the penetration of immune cells, and reinstate anti-tumour immunity. Collectively, these processes indicate that nanocarriers are diverse to be used in improving targeted cancer immunotherapy. Nanobiotechnology has a broad-based solution to enhancing patient outcomes and therapeutic efficacy by promoting checkpoint blockade, vaccine development, cytokine therapy, adoptive cell engineering, and tumor microenvironment modulation.

Mechanisms of nanocarrier-enabled immunotherapy

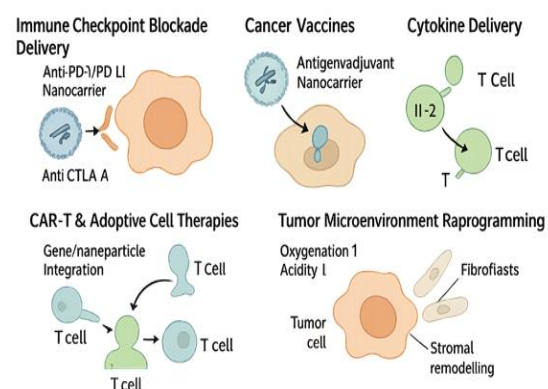


Fig. 2: Mechanisms of nanocarrier-enabled immunotherapy.

Smart nanocarriers can facilitate checkpoint blockade delivery, enhance cancer vaccine efficacy through antigen/adjuvant co-delivery, support cytokine release (e.g., IL-2), improve CAR-T and adoptive cell therapies via gene/nanoparticle integration, and reprogram the tumor microenvironment through oxygenation, acidity modulation, and stromal remodeling.

5. Clinical Translation and Case Studies

This is because the translation of nanobiotechnology-based delivery systems in preclinical models to clinical practice has really gained a pace in the recent years, especially due to the success of lipid nanoparticle (LNP)-based vaccines. Based on the worldwide experience of mRNA vaccines, LNP platforms are currently being

explored in cancer immunotherapy, and there are clinical trials of personalized mRNA cancer immunotherapy with neoantigen-targeting mRNA vaccines. The first findings have shown encouraging activation of the immune system and treatment of tumors, which marks how nanocarriers systems can transform clinical practice. Nanotechnology in cancer immunotherapy is a viable idea that can be demonstrated by several success stories. Application in nanoscale drug delivery Nanoscale drug delivery is finding clinical acceptance due to liposomal formulations of doxorubicin and other chemotherapeutics. Nanoparticle cancer vaccines have recently progressed to phase I and II trials, where they are safe and immunogenic. Moreover, polymeric and inorganic nanocarriers are now in clinical trials to deliver checkpoint inhibitors and cytokines to a specific target site in the body, but the results are still inconsistent with respect to tumor type and patient response.

Although these have been made, even failures have been reported, which is mostly related to low efficacy in the heterogeneous patient population, rapid clearance of nanoflake or unexpected toxicity. Nanotechnology has proven challenging in extending nanotechnology beyond academic research through early-phase trials, where many candidates, which demonstrated good preclinical results, failed to advance to later clinical stages. The most critical issues in clinical translation have been regulatory and safety. Re-manufacturability of large-scale production, long haemotoxicity, biodistribution and immunogenicity are some of the issues that should be tackled. There are certain rules that the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) set regarding nanomedicines, but the absence of standardised evaluation models remains a problem. There must hence be close cooperation between the researchers, clinicians and regulatory authorities to see that the nanobiotechnology-based smart delivery platforms would be able to travel safely and proficiently through bench-to-bedside.

6. Challenges and Limitations

As incredible as it sounds, even with the opportunities that nanobiotechnology-based systems of delivering cancer immunotherapy can offer, there are still a number of issues and problems that restrict the widespread application of this type of delivery in clinical environments. The issue of the toxicity and biodegradation of nanocarriers is one of the top priorities. Most lipid- and polymer-based carriers are considered as being biocompatible; however, their safety profiles are unclear in the short term, especially in the case of inorganic and metallic nanoparticles. Chronic

toxicity may result when the accumulation of the drug occurs in off-target organs (liver, spleen, and kidney), whereas incomplete biodegradation may trigger an inflammatory or immune-mediated reaction. The level of creating carriers that are sufficient in terms of stability during circulation and at the same time full and absolute clearance out of the body is a challenge that is still on the go. Another barrier that is critical is the manufacturing scalability. Synthesis on the laboratory scale is typically a multifaceted process with highly demanding conditions which are not easily replicated at a scale corresponding to an industry. To be able to achieve batch-to-batch consistency in size, surface charge and loading of drugs is required to obtain regulatory approval, but often current production methods lack the critical strength needed to produce in large scale. There is an urgent need to develop scalable and cost-effective, as well as Good Manufacturing Practices (GMP)-compliant production methods that will drive the rapid clinical translation. Clinical outcomes are further complicated by the fact that the immune clearance and the possibility of tumor heterogeneity are the problems. Nanocarriers may be efficiently identified and absorbed promptly by the mononuclear phagocyte system leading to shorter circulation times and treatment effector in the tumors. In addition, the high variability of tumors, which is manifested in differences in the density of vascularity, stromal constituents, and the presence of immune cells makes the homogeneous penetration of nanocarriers limited. This heterogeneity also adds up to irregular therapeutic responses in patients and the different types of cancers, and this necessitates individual design approaches.

Lastly, absence of long-term clinical data is also a major limitation. Even though there are a number of biomedical studies in which the nanocarrier-based immunotherapies were applied in the early phase due to their safety and immunogenicity, only a small number of them were followed up in the long term of their development. There is a paucity of understanding regarding long-term effects in terms of survival advantages, immune response durability and the likelihood of delayed toxicity. In the absence of strong longitudinal data, the regulatory authority and clinicians stand on their feet to support extensive clinical application. To focus on these concerns, there is a need to work interdisciplinarily and combine the progress of material science, immunology, bioengineering and clinical oncology. It will be necessary to overcome the problem of safety, scalability, biological constraints as well as availability of data in order to open up the full potential of nanobiotechnology in targeted cancer immunotherapy.

7. Future Directions

Future perspectives of nanobiotechnology in cancer immunotherapy is a combination of superior engineering strategies with precision medicine, which will eliminate the status quo and unleash groundbreaking clinical results. Among the potential opportunities is the creation of AI-controlled nanocarrier. Prediction of nanoparticle based on machine learning and computational models is being used more and more to predict nanoparticle-biological interactions, optimize physicochemical properties, and predict the patterns of biodistribution. With the help of these approaches, it will be possible greatly shorten the design cycle, lower the costs of experiments, and increase the chances of effective clinical translation because nanocarriers can be personalized. The development of personalized nanomedicine is another important highlight on the possibilities of streamlining delivery systems to the profile of a single patient. With nanocarriers, it is also possible to create custom antigen cocktails, checkpoint inhibitors, or cytokine combinations tailored to the tumor and immune landscape of a particular patient by utilizing the genomic, proteomic, and immunological information. This individualization can improve both the effectiveness and decrease individual differences in response to treatment. Another frontier is the introduction of hybrid bio-synthetic smart carriers. When synthetic nanomaterials are coupled with biological components, including cell membranes, exosomes, or engineered proteins, then one can gain synergistic benefits, which are the stability of synthetic systems as well as the biocompatibility and immune-evasive characteristics of biological structures. These hybrid systems come with potential of multifunctional delivery, better targeting as well as less systemic toxicity.

Lastly, the clinical decision-making is likely to be redefined with the incorporation of the digital twin and precision oncology frameworks. Digital twin models: It may be possible using digital twin model, which are virtual patient-specific models of clinical and molecular data interacting in real-time to predict the results of therapeutics, the optimization of dosing regimen, and selection of nanocarrier-based immunotherapy. Combining nanobiotechnology and precision oncology tools can produce oncological adaptive plans, which will keep changing as the disease advances. All these future directions point to a change towards intelligent, patient-centered, and data-driven nanomedicine. The future generation of smarter delivery platforms has the potential to achieve the entirety of the promise of cancer immunotherapy by bringing together innovations in the field of

computational design, personalized therapy, hybrid material development, and digital health.

8. CONCLUSION

Nanobiotechnology is also uniquely shaping immune therapeutic approaches to tumour neuroinvasions through the provision of novel delivery platforms that are more precise, more effective, and more safe. With the solutions of intelligent nanocarriers, one can now address the most annoying issues like poor biodistribution, immune evasion, and systemic toxicity hence, establishing new potentials of lasting and patient-specific cancer therapies. Nonetheless, bench to bedside translations cannot be done successfully with only technological innovation. It requires interdisciplinary fusion, combines nanotechnological, immunological, oncological, materials science and computational modeling progress. Restrictive liaisons of researchers, clinicians, and the regulatory bodies will be necessary to allow the resolution of the issues corresponding to the safety, scalability, and long-term effectiveness. The delivery platforms that are facilitated by nanobiotechnology will help not only complement the current cancer immunotherapy strategies, that are enabled by nanobiotechnology, but also greatly contribute to them. These systems have the potential to take precision oncology and enhance the survival of affected patients across the world with further innovation and stringent clinical validation.

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