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Mini Review

Nanomedicine-Driven Advances: Enhancing Checkpoint Inhibition and CAR-T Therapies in Cancer Immunotherapy

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Abstract

Cancer immunotherapy has revolutionized oncological treatment, offering patients improved survival and quality of life. However, tumor heterogeneity, immune evasion, and treatment toxicity hinder its full potential. Nanomedicine provides innovative solutions to these challenges by enhancing immunotherapeutic strategies' efficacy, specificity, and safety. This review explores current advances in the application of nanomaterials in cancer immunotherapy, focusing on their role in personalized approaches, multifunctional therapeutic modalities, biocompatibility considerations, and enhancement of the enhanced permeability and retention (EPR) effect. Critical developments in bioinspired and stimuli-responsive nanotechnologies are discussed, emphasizing their ability to modulate the tumor microenvironment (TME), improve drug delivery, and facilitate combination therapies. The review also addresses translational challenges, regulatory considerations, and clinical advancements, highlighting examples from recent clinical trials and emerging technologies. Personalized nanomedicine enables the design of tailored therapeutic agents targeting tumors, reducing off-target effects and maximizing therapeutic efficacy. Multifunctional nanomaterials facilitate synergistic effects when combining photothermal, photodynamic, chemotherapeutic, and immunotherapeutic modalities. While promising, toxicity, biodegradability, and long-term safety issues necessitate standardized evaluation protocols for clinical translation. Advancements in stimuli-responsive nanomaterials and immune checkpoint inhibitors contribute to developing next-generation cancer immunotherapies with improved outcomes. This review provides a comprehensive overview of nanomedicine's current landscape, challenges, and future perspectives in cancer immunotherapy, advocating for further research to address the existing gaps and optimize clinical applications.

Keywords: Nanomedicine; immunotherapy; nanoparticles; tumor microenvironment; immune checkpoint inhibitors; drug delivery systems

Introduction

Cancer immunotherapy has revolutionized oncological treatment recently, offering new hope for improved survival and disease management. Among the most notable advances are immune checkpoint inhibitors (ICIs) and chimeric antigen receptor T-cell (CAR-T) therapies, which have shown unprecedented clinical efficacy across various malignancies [1-3]. However, these therapies face significant challenges, including limited efficacy in certain tumor types, toxicities such as immune-related adverse events, and heterogeneous patient responses, all underscoring the need for improved therapeutic strategies [4-6]. Nanomedicine is a promising approach to address these limitations, offering novel opportunities for targeted drug delivery, enhanced immunomodulation, and improved treatment outcomes [7-9]. The limitations of current immunotherapeutic approaches are multi-faceted. The specificity of ICIs and CAR-T therapies remains challenging, as the complex and diverse tumor microenvironment (TME) can hinder their effectiveness [10,11]. The lack of uniform biomarkers across different tumors complicates patient stratification and therapeutic targeting, limiting the broader applicability of these treatments [6].

Although effective in hematologic malignancies, CAR-T therapies have shown limited success in solid tumors due to poor tumor penetration, antigen heterogeneity, and immunosuppressive TME [12-14]. Furthermore, systemic toxicities and adverse immune responses pose significant barriers to widespread clinical use [5,15]. Nanomedicine presents a strategy to overcome these challenges by enabling the targeted delivery of therapeutics directly to the tumor site, reducing off-target effects and systemic toxicity [10,16]. Nanomaterials can be engineered to enhance the specificity and efficiency of drug delivery, penetrate the TME, and improve the therapeutic accumulation through the enhanced permeability and retention (EPR) effect [17-19]. Moreover, specific nanomaterials can actively modulate the TME, promote anti-improve immune responses, and overcome drug resistance [1,20-22]. The ability of nanomaterials to carry multiple payloads—such as drugs, genes, or adjuvants—enables combination therapies that simultaneously target tumor cells and modulate the immune response [3,10,23]. Despite these advances, the clinical translation of nanomedicine-based immunotherapies faces challenges, including regulatory, safety, and ethical considerations [11,24-26]. The development of clinically viable nanomedicines requires stringent evaluation of their pharmacokinetics, biodistribution, toxicity, and long-term effects, all of which can vary significantly depending on the size, shape, surface chemistry, and material composition of the nanomaterials used [5,11,27]. The heterogeneity of tumor-specific targets and the impact of patient-specific factors such as genetics, immune status, and the TME on nanomaterial behavior present hurdles for personalized treatment approaches [12,15,28].

One critical gap in nanomedicine research is understanding the biodegradability and long-term clearance of different nanomaterials. Non-biodegradable or poorly degradable nanomaterials pose a risk of accumulation in non-target tissues, which can lead to potential toxicity or immunogenicity over time [29-31]. Hence, the design of nanomaterials with controlled degradability, minimal long-term toxicity, and appropriate clearance from the body remains a priority for safe clinical application [5,32-34]. Another area of concern is the development of resistance to nanomaterial-based immunotherapies. Just as tumor cells can develop resistance to conventional chemotherapy or targeted therapies, they may also acquire mechanisms to evade or counteract nanomedicine-induced immune responses [14,35-37]. Strategies to address this issue include designing multifunctional nanomaterials that can modulate the immune response in various ways, thus reducing the likelihood of resistance [8,15,38]. The immune system itself can pose a challenge to the delivery of nanomedicines, as immune cells may recognize and clear these nanomaterials before they reach the tumor site [39]. Introducing stealth technologies, such as surface PEGylation or cloaking nanomaterials with cell membranes, can help evade immune detection and improve the biodistribution and targeting of the nanocarriers [16,17]. Understanding the interactions between nanomaterials and the host immune system is essential for developing more efficient delivery systems [40-42].

While ICIs and CAR-T therapies have received the most attention in nanomedicine, other immunotherapeutic strategies, such as cancer vaccines, oncolytic viruses, and cytokine-based therapies, also hold the potential for synergistic combinations with nanomaterials [43-45]. Nanomaterials can be engineered to deliver tumor antigens, adjuvants, or immune-modulating agents to enhance vaccine efficacy or to serve as carriers for oncolytic viruses, which can kill tumor cells and stimulate an immune response. Exploring these combinations may expand the scope and effectiveness of nanomedicine-enhanced immunotherapies [20,21]. A crucial aspect often overlooked is the cost-effectiveness and accessibility of nanomedicine-based therapies. Nanomaterials' production, characterization, and regulatory approval can be complex and costly, raising concerns about their affordability and scalability, particularly in low- and middle-income settings. Addressing these economic and logistical challenges is vital to ensure that the benefits of nanomedicine reach a broader patient population [5,46-48].

Ongoing research into novel nanomaterials such as metal-organic frameworks, exosome-based nanocarriers, and self-assembling biomaterials is rapidly expanding the arsenal of tools available for cancer immunotherapy [15]. These emerging materials offer unique properties that could improve nanomedicine-based immunotherapies' efficacy, targeting, and safety, emphasizing the need to explore new nanotechnology platforms continuously [3,49-51]. This review aims to provide a comprehensive overview of the current advances in nanomedicine for cancer immunotherapy. It focuses on the use of nanomaterials to enhance the efficacy of existing immunotherapies, overcome resistance, and improve the precision and safety of treatment. This highlights the translational challenges and future directions in integrating nanomedicine into cancer immunotherapy by addressing the gaps above and exploring the potential of novel nanomaterial-based strategies.

Methods

This integrative literature review explored the role of nanomedicine in enhancing cancer immunotherapy. A thorough search was conducted across multiple databases, including PubMed, Scopus, Embase, Web of Science, SciELO, and Google Scholar, to ensure a comprehensive collection of relevant literature. The search strategy utilized a combination of specific keywords and Boolean operators to optimize retrieval. Key terms included "nanomedicine," "cancer immunotherapy," "nanoparticles," "immune checkpoint inhibitors," "tumor microenvironment," and "drug delivery systems." Boolean operators (AND, OR) were employed to refine research and ensure that all topic aspects were captured, focusing on therapeutic mechanisms, clinical applications, and safety considerations. The review included diverse study designs, such as randomized controlled trials, cohort studies, case-control studies, cross-sectional analyses, case series, systematic reviews, meta-analyses, and preclinical studies. Eligible studies are needed to address nanomaterials' applications in cancer immunotherapy, focusing on mechanisms of action, clinical outcomes, or their combined use with other treatments. Study selection was performed independently by two reviewers who screened titles and abstracts to identify relevant studies. A third independent reviewer resolved any disagreements. All reviewers were blinded to the details of the studies to maintain an unbiased selection process. Data extraction was conducted using a standardized form, collecting key details like authorship, publication year, study design, population or model characteristics, interventions, and outcomes related to nanomaterial use in cancer immunotherapy. The primary focus was on how nanomaterials modulate immune responses, enhance drug delivery, interact with the tumor microenvironment, and integrate with other immunotherapeutic modalities. A qualitative synthesis approach was employed, using thematic analysis to categorize and integrate findings. This review aimed to identify advances, challenges, and gaps in the field, considering practical aspects such as safety, regulatory hurdles, and the translational potential of nanomedicine in clinical oncology. The conclusions reflect a critical synthesis of the literature, providing a clear overview of the role of nanomedicine in cancer immunotherapy.

Results and Discussion

Nanomedicine has emerged as a transformative approach in cancer immunotherapy, addressing the limitations of traditional treatments by enhancing efficacy, specificity, and safety [52]. The advent of nanomaterials, such as liposomes, dendrimers, polymeric nanoparticles, and metal-organic frameworks (MOFs), has opened novel strategies for the delivery of therapeutic agents [37]. Their unique properties—such as small size, tunable surface characteristics, and high drug-loading capacities—allow for the development of more targeted and individualized treatment regimens [53-55]. Moreover, they enable the modulation of the tumor microenvironment (TME), a critical factor in improving the response to immunotherapies like checkpoint inhibitors and CAR-T cell therapies [56]. This review provides a comprehensive overview of the role of nanomaterials in cancer immunotherapy, exploring current developments, challenges, and future directions. Topics include personalized nanomedicine, multifunctional nanomaterials, biocompatibility concerns, enhancement of the enhanced permeability and retention (EPR) effect, and recent regulatory and clinical advancements [28,57].

Personalized Approaches in Nanomedicine

A cornerstone of modern cancer treatment is the ability to tailor therapies to the individual patient. Precision medicine has paved the way for designing nanomaterials that specifically target molecular markers of tumor cells [58-60]. These customizable nanoplatforms, including functionalized liposomes, dendrimers, and polymeric nanoparticles, have shown great promise in adapting to tumors' molecular and genetic landscape, enhancing the specificity and efficacy of immunotherapeutic agents [3,61-63]. For instance, functionalized nanoparticles coated with targeting ligands can recognize overexpressed receptors on cancer cells, facilitating the selective delivery of drugs while sparing healthy tissues [39,64-66]. Recent developments have focused on incorporating personalized nanomedicine into immunotherapy protocols, including CAR-T cell therapies and immune checkpoint inhibitors [67]. A prime example is using tumor-specific antigens to develop nano vaccines that trigger potent and tailored anti-tumor immune responses while minimizing systemic side effects [68-70]. Additionally, engineering patient-derived exosomes, naturally occurring cell-derived vesicles, presents an innovative approach. These exosomes can be loaded with immune adjuvants to enhance tumor immunogenicity and improve immunotherapeutic outcomes [12,64,71]. A key advantage of nanomedicine in personalized immunotherapy is its ability to overcome tumor heterogeneity, a significant challenge in achieving consistent treatment responses across patient populations [72-74]. Nanoparticles can be engineered to carry multiple therapeutic agents simultaneously, allowing for combinational delivery that targets various tumor pathways. For example, dendrimers have been explored as nanocarriers for siRNA, monoclonal antibodies, and chemotherapeutics, providing a multifaceted approach to disrupt tumor growth and induce an immune response [50,75,76].

Multifunctional Nanomaterials for Combined Therapies

Nanomaterials designed to carry out multiple therapeutic functions have garnered significant attention due to their ability to integrate diverse treatment modalities [78]. These multifunctional platforms offer the capability to combine photothermal therapy (PTT), photodynamic therapy (PDT), chemotherapy, and immunotherapy to create a comprehensive anti-cancer strategy [7,23,79-81]. Multifunctional nanoparticles are particularly advantageous for addressing the complexity of cancer and its ability to evade singular treatment approaches [82]. PTT and PDT utilize external stimuli, such as near-infrared light, to generate localized heat or reactive oxygen species that destroy tumor cells. Combined with nanomaterials, these therapies enhance the tumor's susceptibility to immune cell infiltration [83-85]. This transformation of the TME—converting "cold" tumors, which have low immunogenicity, into "hot" tumors, which are highly responsive to immune attack—has demonstrated considerable promise

in preclinical studies [47,60,86]. Moreover, stimuli-responsive nanoparticles that release chemotherapeutic agents in response to specific tumor signals provide a dual effect: direct tumor cell killing and activation of systemic immune responses [45,75,87].

Recent developments have also explored magnetically responsive nanoparticles that deliver drugs in a controlled manner to the tumor site, further improving site-specific delivery while minimizing systemic toxicity [88-90]. Combining nanomaterials with chemotherapy drugs, immunostimulatory agents, and PTT or PDT provides a robust and synergistic anti-tumor response, enhancing overall treatment efficacy [91,92].

Toxicity and Biocompatibility Considerations

The clinical translation of nanomedicine hinges on ensuring the safety and biocompatibility of nanomaterials. Despite their therapeutic potential, nanomaterials may pose risks of long-term accumulation, off-target immune activation, and interactions with non-target organs [10,39,93]. Studies have shown that metal-based nanoparticles, such as gold or silver, can induce oxidative stress, provoke inflammation, or elicit undesired immune responses. Therefore, optimizing nanoparticles' surface characteristics, size, and charge is essential for mitigating toxicity and enhancing therapeutic index [53, 83,94-96]. Biodegradable nanomaterials, such as lipid-based or polymer-based nanoparticles, represent a more biocompatible alternative as they degrade into non-toxic byproducts over time [97-99]. Their degradation rate, however, must be carefully balanced to achieve efficient drug delivery and timely clearance from the body, thereby avoiding prolonged exposure and potential toxicity [55,100-102]. For example, PEGylation—a process of coating nanoparticles with polyethylene glycol—can improve the circulation time of nanoparticles while reducing their immunogenicity [81,103-105]. Standardized protocols and biosafety assessment guidelines are critical to evaluating the long-term effects of nanomaterials on the immune system and ensuring their safe integration into clinical practice [22,106].

Enhancing the Enhanced Permeability and Retention (EPR) Effect

A pivotal aspect of targeted drug delivery in nanomedicine is the exploitation of the EPR effect, which allows nanoparticles to accumulate in tumor tissues due to the leaky vasculature and poor lymphatic drainage associated with tumors [107]. However, the variability of the EPR effect across different tumor types poses challenges for the consistent delivery of nanotherapeutics [40,68]. Some tumors, characterized by dense stroma or insufficient vasculature, exhibit limited nanoparticle penetration, reducing the effectiveness of drug delivery [38]. Researchers are exploring approaches to enhance the effect of EPR to overcome these challenges. Strategies such as the modulation of the TME to increase vascular permeability, using smaller or deformable nanoparticles to facilitate tumor penetration, and applying external stimuli to trigger drug release are being actively investigated [67,105,108]. Stimuli-responsive nanoparticles, which can alter their properties in response to specific changes in the TME—such as pH, temperature, or enzyme activity, provide a targeted approach to drug delivery and improve the precision of therapy [42,93].

Innovations in Bioinspired and Stimuli-Responsive Nanotechnologies

The latest advances in bioinspired and stimuli-responsive nanotechnologies have propelled the development of sophisticated drug delivery systems. Bioinspired nanomaterials, such as cell membrane-coated nanoparticles, have shown enhanced biocompatibility, prolonged circulation times, and improved targeting capabilities due to their biomimetic properties [11,102]. The use of immune cell-derived vesicles for coating nanoparticles has further demonstrated potential in promoting immune evasion and enhancing tumor-specific delivery [5,15,22]. Additionally, stimuli-responsive nanomaterials are engineered to respond to external and internal cues, such as pH changes, light, temperature, or enzymatic activity, enabling controlled and on-demand drug release [20,57]. With their high drug-loading capacity and tunable porosity, MOFs have been employed to deliver immune checkpoint inhibitors and promote immunogenic cell death [39]. Polymersomes, vesicular structures formed from amphiphilic block copolymers, have also been developed to enhance the specificity and efficacy of cancer immunotherapies [92,42,109]. Gene-editing tools like CRISPR-Cas9 have recently been incorporated into nanoparticle delivery systems to modulate immune pathways and enhance the targeting of cancer cells. The development of theragnostic nanomaterials—capable of simultaneous therapy and diagnostics—has further expanded the applications of nanomedicine, offering real-time monitoring of therapeutic responses and personalized adjustments in treatment regimens [62,89,99].

Current Challenges in Cancer Immunotherapy

Despite the progress in immunotherapy, challenges such as systemic toxicity, limited tumor penetration, and heterogeneous responses among patients continue to limit therapeutic success. While revolutionary, immune checkpoint inhibitors and CAR-T cell therapies are not universally effective due to the immunosuppressive TME, which causes many tumors to develop, limiting immune cell infiltration and function [5,6,8]. The financial and logistical complexities of CAR-T cell manufacturing, combined with the risk of severe side effects like CRS, highlight the need for alternative strategies to broaden the therapeutic window and improve the safety of immunotherapies [19,96,110]. Nanomaterials offer a means to enhance the efficacy and safety of immunotherapies by improving the targeting of tumor cells, promoting immune cell activation, and reducing off-target effects. For example, nanoparticles loaded with PD-1/PD-L1 inhibitors can localize the immune checkpoint blockade effect to the TME, improving immune cell function while minimizing systemic toxicity [21,60].

Translational Challenges and Clinical Implications

The journey from bench to bedside for nanomaterials in cancer immunotherapy is complex, requiring the careful optimization of nanoparticle synthesis, scale-up processes, and batch reproducibility [55,80]. Ensuring consistent efficacy

and safety across different patient populations is critical, as is understanding how nanomaterials interact with the immune system over time. The immunogenicity of nanomaterials must be carefully evaluated to avoid unwanted immune activation or suppression [55,111]. Regulatory agencies like the FDA and EMA have established nanoparticle characterization, pharmacokinetics, and toxicity guidelines. However, the approval pathways for nanomaterial-based therapeutics remain intricate due to the need for standardized methods to evaluate safety and efficacy. The approval of PEGylated liposomal doxorubicin (Doxil®) marked a milestone in nanomedicine, but it also highlighted the need for comprehensive safety assessments of biodistribution, clearance mechanisms, and immune system interactions [10,80,85].

Clinical Trials and Translational Advances

A growing number of clinical trials are evaluating the efficacy of nanomaterials in cancer immunotherapy. For instance, pembrolizumab-loaded nanoparticles for melanoma and renal cell carcinoma (NCT03897036) have enhanced therapeutic responses and reduced side effects. Moreover, nanoparticle-based vaccines for HPV-associated cancers (NCT03418480) have shown promising immunogenicity and safety profiles [38,72]. These trials illustrate the potential of nanomaterials to improve immune activation and tumor targeting while reducing adverse effects. Combination therapies that utilize NDDSs with PTT, PDT, and immune checkpoint blockade have demonstrated increased immune cell infiltration and improved overall response rates in solid tumors [45,86]. Such advancements underscore the potential for integrating nanomaterials into current immunotherapy regimens for more robust and effective cancer treatments [66,78].

Nanomedicine-Based Drug Delivery Systems (NDDSs)

NDDSs have revolutionized the delivery of immunotherapeutic agents by ensuring targeted and controlled release within the tumor microenvironment. Stimuli-responsive NDDSs are particularly advantageous for releasing therapeutic payloads in response to specific environmental changes in the TME, such as pH and temperature variations [22,41]. For instance, pH-sensitive nanoparticles have been engineered to release immune checkpoint inhibitors within acidic tumor sites, maximizing the therapeutic impact while minimizing systemic exposure [35,92]. The use of NDDSs in combination with traditional treatments like chemotherapy and radiotherapy has demonstrated synergistic effects. Nanocarriers that co-deliver chemotherapeutic agents and immune modulators have enhanced antitumor activity by simultaneously promoting tumor cell death and activating immune responses [2,37]. These approaches are being explored in clinical settings to improve treatment outcomes in cancers resistant to monotherapy [26,59].

Combination Strategies of Nanomaterials and Immunotherapies

Combining nanomaterials with established immunotherapies has opened new avenues for enhancing treatment efficacy. Nanoparticles designed to deliver cytokines, co-stimulatory molecules, or genetic material to the TME have shown potential in augmenting the effects of CAR-T cells and checkpoint inhibitors [6,19]. These strategies facilitate the expansion and persistence of immune cells within the TME, overcoming immunosuppression and improving therapeutic outcomes. Peptide-functionalized nanoparticles represent a promising approach to enhance the targeting of tumor antigens and improve antigen presentation, thereby boosting T-cell activation and antitumor responses [7,46]. These innovative combinations leverage the strengths of both nanotechnology and immunotherapy to develop highly targeted and potent cancer treatments [96].

Regulatory Considerations and Safety Assessment of Nanomedicine

Ensuring the safety of nanomaterial-based immunotherapies is crucial for their clinical advancement. While PEGylated liposomal doxorubicin has set a precedent for regulatory approval, the path to approval is often challenging due to stringent safety assessments, particularly regarding biodistribution, immune response potential, and biodegradability [10,85]. Regulatory agencies have focused on developing comprehensive guidelines to ensure that nanomaterials possess predictable biological behavior, minimal off-target effects, and consistent manufacturing processes [25,55]. The development of standardized protocols for safety and efficacy evaluations, including the impact of nanoparticle size, shape, and surface characteristics, is vital for advancing nanomaterial-based immunotherapies [112]. Biocompatibility studies must assess whether nanoparticles induce adverse immune reactions or accumulate tissues to toxic levels over time and consider how different patient populations may respond to these therapies [53,106].

Future Directions and Emerging Trends

The future of nanomedicine in cancer immunotherapy is marked by emerging trends in bioinspired materials, such as cell membrane-coated nanoparticles, which enhance targeting specificity, immune evasion, and biocompatibility [56,102]. Stimuli-responsive nanomaterials, designed to react to endogenous and exogenous signals for controlled drug release, offer new opportunities for precision medicine applications [11,92]. Advances in genetic engineering enable the development of nanocarriers with enhanced targeting capabilities and therapeutic efficacy, opening the door to next-generation cancer immunotherapies [20,62]. Critical areas for future research include addressing gaps in understanding nanomaterials' long-term safety and pharmacokinetics, optimizing manufacturing scalability, and navigating complex regulatory pathways [24,60]. Collaborative efforts between academia, industry, and regulatory bodies, along with rigorous clinical trials, will be pivotal in advancing the field of nanomedicine and realizing its full potential in revolutionizing cancer immunotherapy [43,81].

Conclusion

Nanomedicine has significantly advanced cancer immunotherapy, providing innovative strategies to enhance existing treatments' specificity, efficacy, and safety. Personalized nanomaterials offer the

ability to tailor therapies to the unique molecular characteristics of individual tumors, improving treatment outcomes and minimizing side effects. Multifunctional nanomaterials integrate diverse therapeutic modalities to overcome the complexities of tumor heterogeneity and immunosuppressive TME. Advances in stimuli-responsive and bioinspired nanotechnologies further enhance the precision and efficacy of immunotherapies. However, challenges remain in understanding the long-term safety of nanomaterials, optimizing their clinical translation, and navigating regulatory pathways. The growing number of clinical trials and translational studies highlights the potential of nanomedicine to transform cancer treatment. By addressing existing gaps and leveraging collaborative research, nanomaterials are poised to revolutionize cancer immunotherapy, offering promising avenues for improved patient outcomes and personalized care.

Continued innovation in nanotechnology and its integration into immunotherapy holds the potential to make a lasting impact on the management and cure of cancer.

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Conflict of Interest

The authors declare that there is no conflict of interest.

References

1. Peng S, Xiao F, Chen M, Gao H (2022) Tumor-Microenvironment-Responsive Nanomedicine for Enhanced Cancer Immunotherapy. Adv Sci (Weinh) 9(1).
2. Pei Z, Chen S, Ding L, Liu J, Cui X, et al. (2022) Current perspectives and trend of nanomedicine in cancer: A review and bibliometric analysis. J Control Release 352: 211-241.
3. Yang Y, Huang J, Liu M, Qiu Y, Chen Q, et al. (2023) Emerging Sonodynamic Therapy-Based Nanomedicines for Cancer Immunotherapy. Adv Sci (Weinh)10(2).
4. Ashrafizadeh M, Zarrabi A, Bigham A, Taheriazam A, Saghari Y, et al. (2023) (Nano)platforms in breast cancer therapy: Drug/gene delivery, advanced nanocarriers and immunotherapy. Med Res Rev 43(6): 2115-2176.
5. Cabral H, Kinoh H, Kataoka K (2020) Tumor-Targeted Nanomedicine for Immunotherapy. Acc Chem Res 53(12): 2765-2776.
6. Gong N, Sheppard NC, Billingsley MM, June CH, Mitchell MJ (2021) Nanomaterials for T-cell cancer immunotherapy. Nat Nanotechnol 16(1): 25-36.
7. Fu Y, Bian X, Li P, Huang Y, Li C (2022) Carrier-Free Nanomedicine for Cancer Immunotherapy. J Biomed Nanotechnol 18(4): 939-956.
8. Gupta J, Safdari HA, Hoque M (2021) Nanoparticle mediated cancer immunotherapy. Semin Cancer Biol 69: 307-324.
9. Yang Z, Gao D, Zhao J, Yang G, Guo M, et al. (2023) Thermal immuno-nanomedicine in cancer. Nat Rev Clin Oncol 20(2): 116-134.
10. Guo S, Feng J, Li Z, Yang S, Qiu X, et al. (2023) Improved cancer immunotherapy strategies by nanomedicine. Wiley Interdiscip Rev Nanomed Nanobiotechnol 15(3).
11. Bockamp E, Rosigkeit S, Siegl D, Schuppan D (2020) Nano-Enhanced Cancer Immunotherapy: Immunology Encounters Nanotechnology. Cells 9(9): 2102.
12. Khan MM, Li Y, Zhou Z, Ni A, Saiding Q, et al. (2024) Macrophage-modulating nanomedicine for cancer immunotherapy. Nanoscale 16(15): 7378-7386.
13. Martin JD, Miyazaki T, Cabral H (2021) Remodeling tumor microenvironment with nanomedicines. Wiley Interdiscip Rev Nanomed Nanobiotechnol 13(6).
14. Yang R, Chen L, Wang Y, Zhang L, Zheng X, et al. (2023) Tumor microenvironment responsive metal nanoparticles in cancer immunotherapy. Front Immunol 14: 1237361.
15. Gowd V, Ahmad A, Tarique M, Suhail M, Zughaibi TA, et al. (2022) Advancement of cancer immunotherapy using nanoparticles-based nanomedicine. Semin Cancer Biol 86(Pt 2): 624-644.
16. Ma X, Li SJ, Liu Y, Zhang T, Xue P, et al. (2022) Bioengineered nanogels for cancer immunotherapy. Chem Soc Rev 51(12): 5136-5174.
17. Xiong Y, Wang Y, Tiruthani K (2019) Tumor immune microenvironment and nano-immunotherapeutics in colorectal cancer. Nanomedicine 21: 102034.
18. Han Y, Wen P, Li J, Kataoka K (2022) Targeted nanomedicine in cisplatin-based cancer therapeutics. J Control Release 345: 709-720.
19. Guevara ML, Persano F, Persano S (2021) Nano-immunotherapy: Overcoming tumour immune evasion. Semin Cancer Biol 69: 238-248.
20. Liu J, Liew SS, Wang J, Pu K (2022) Bioinspired and Biomimetic Delivery Platforms for Cancer Vaccines. Adv Mater 34(1).
21. Boone CE, Wang L, Gautam A, Newton IG, Steinmetz NF (2022) Combining nanomedicine and immune checkpoint therapy for cancer immunotherapy. Wiley Interdiscip Rev Nanomed Nanobiotechnol 14(1).
22. Comparetti EJ, Ferreira NN, Ferreira LMB, Kaneno R, Zucolotto V (2022) Immunomodulatory properties of nanostructured systems for cancer therapy. J Biomed Mater Res A 110(5): 1166-1181.
23. Desai N, Chavda V, Singh TRR, Thorat ND, Vora LK (2024) Cancer Nanovaccines: Nanomaterials and Clinical Perspectives. Small 20(35).
24. Jin Y, Huang Y, Ren H, Huang H, Lai C, et al. (2024) Nano-enhanced immunotherapy: Targeting the immunosuppressive tumor microenvironment. Biomaterials 305: 122463.
25. Zhao YD, Muhetaerjiang M, An HW, Fang X, Zhao Y, et al. (2021) Nanomedicine enables spatiotemporally regulating macrophage-based cancer immunotherapy. Biomaterials 268: 120552.
26. Zhang P, Zhai Y, Cai Y, Zhao Y, Li Y (2019) Nanomedicine-Based Immunotherapy for the Treatment of Cancer Metastasis. Adv Mater 31(49).
27. Li X, Guo X, Ling J, Tang Z, Huang G, et al. (2021) Nanomedicine-based cancer immunotherapies developed by reprogramming tumor-associated macrophages. Nanoscale 13(9): 4705-4727.
28. Sun B, Hyun H, Li LT, Wang AZ (2020) Harnessing nanomedicine to overcome the immunosuppressive tumor microenvironment. Acta Pharmacol Sin 41(7): 970-985.
29. Zhao Y, Bilal M, Qindeel M, Khan MI, Dhama K, et al. (2021) Nanotechnology-based immunotherapies to combat cancer metastasis. Mol Biol Rep 48(9): 6563-6580.
30. Zhang C, Pu K (2020) Molecular and nanoengineering approaches towards activatable cancer immunotherapy. Chem Soc Rev 49(13): 4234-4253.
31. Jiang Z, Zhang W, Zhang J, Liu T, Xing J, et al. (2022) Nanomaterial-Based Drug Delivery Systems: A New Weapon for Cancer Immunotherapy. Int J Nanomedicine 17: 4677-4696.

32. Li W, Peng A, Wu H, Quan Y, Li Y, et al. (2020) Anti-Cancer Nanomedicines: A Revolution of Tumor Immunotherapy. Front Immunol 11: 601497.

33. Zhang J, Lin Y, Lin Z, Wei Q, Qian J, et al. (2022) Stimuli-Responsive Nanoparticles for Controlled Drug Delivery in Synergistic Cancer Immunotherapy. Adv Sci (Weinh) 9(5).

34. Han S, Huang K, Gu Z, Wu J (2020) Tumor immune microenvironment modulation-based drug delivery strategies for cancer immunotherapy. Nanoscale 12(2): 413-436.

35. Lu L, Sun Y, Wan C, Hu Y, Lo PC, et al. (2021) Role of intravital imaging in nanomedicine-assisted anti-cancer therapy. Curr Opin Biotechnol 69: 153-161.

36. Wang Y, Huang G, Hou Q, Pan H, Cai L (2023) Cell surface-nanoengineering for cancer targeting immunoregulation and precise immunotherapy. Wiley Interdiscip Rev Nanomed Nanobiotechnol 15(4).

37. Liu Q, Zhang W, Jiao R, Lv Z, Lin X, et al. (2022) Rational Nanomedicine Design Enhances Clinically Physical Treatment-Inspired or Combined Immunotherapy. Adv Sci (Weinh) 9(29).

38. Martin JD, Cabral H, Stylianopoulos T, Jain RK (2020) Improving cancer immunotherapy using nanomedicines: progress, opportunities and challenges. Nat Rev Clin Oncol 17(4): 251-266.

39. Li Q, Liu Y, Zhang Y, Jiang W (2022) Immunogenicity-boosted cancer immunotherapy based on nanoscale metal-organic frameworks. J Control Release 347: 183-198.

40. Guo Y, Hu P, Shi J (2024) Nanomedicine Remodels Tumor Microenvironment for Solid Tumor Immunotherapy. J Am Chem Soc 146(15): 10217-10233.

41. Jia R, Teng L, Gao L, Su T, Fu L, et al. (2021) Advances in Multiple Stimuli-Responsive Drug-Delivery Systems for Cancer Therapy. Int J Nanomedicine 16: 1525-1551.

42. Mi P (2020) Stimuli-responsive nanocarriers for drug delivery, tumor imaging, therapy and theranostics. Theranostics 10(10): 4557-4588.

43. Yoo YJ, Lee CH, Park SH, Lim YT (2022) Nanoparticle-based delivery strategies of multifaceted immunomodulatory RNA for cancer immunotherapy. J Control Release 343: 564-583.

44. Vincent MP, Navidzadeh JO, Bobbala S, Scott EA (2022) Leveraging self-assembled nanobiomaterials for improved cancer immunotherapy. Cancer Cell 40(3): 255-276.

45. Zafar A, Hasan M, Tariq T, Dai Z (2022) Enhancing Cancer Immunotherapeutic Efficacy with Sonotheranostic Strategies. Bioconjug Chem 33(6): 1011-1034.

46. Dai J, Ashrafizadeh M, Aref AR, Sethi G, Ertas YN (2024) Peptide-functionalized, -assembled and -loaded nanoparticles in cancer therapy. Drug Discov Today 29(7): 103981.

47. Xie L, Li J, Wang L, Dai Y (2023) Engineering metal-phenolic networks for enhancing cancer therapy by tumor microenvironment modulation. Wiley Interdiscip Rev Nanomed Nanobiotechnol 15(3).

48. Ni H, Xue J, Wang F, Sun X, Niu M (2021) Nanomedicine Approach to Immunotherapy of Hepatocellular Carcinoma. J Biomed Nanotechnol 17(5): 771-792.

49. Guo R, Liu Y, Xu N, Ling G, Zhang P (2022) Multifunctional nanomedicines for synergistic photodynamic immunotherapy based on tumor immune microenvironment. Eur J Pharm Biopharm 173:103-120.

50. Yang EL, Sun ZJ (2024) Nanomedicine Targeting Myeloid-Derived Suppressor Cells Enhances Anti-Tumor Immunity. Adv Healthc Mater 13(9).

51. Li Y, Gao Y, Zhang X, Guo H, Gao H (2020) Nanoparticles in precision medicine for ovarian cancer: From chemotherapy to immunotherapy. Int J Pharm 591: 119986.

52. Pan X, Ni S, Hu K (2024) Nanomedicines for reversing immunosuppressive microenvironment of hepatocellular carcinoma. Biomaterials 306: 122481.

53. Zhu D, Zhu XH, Ren SZ, Lu YD, Zhu HL (2021) Manganese dioxide (MnO2) based nanomaterials for cancer therapies and theranostics. J Drug Target 29(9): 911-924.

54. Sun W, Xie S, Liu SF, Hu X, Xing D (2024) Evolving Tumor Characteristics and Smart Nanodrugs for Tumor Immunotherapy. Int J Nanomedicine 19: 3919-3942.

55. García Domínguez DJ, López Enríquez S, Alba G, Garnacho C, Jiménez Cortegana C, et al. (2024) Cancer Nano-Immunotherapy: The Novel and Promising Weapon to Fight Cancer. Int J Mol Sci 25(2): 1195.

56. Raza F, Zafar H, Zhang S, Kamal Z, Su J, et al. (2021) Recent Advances in Cell Membrane-Derived Biomimetic Nanotechnology for Cancer Immunotherapy. Adv Healthc Mater 10(6).

57. Li Q, Liu X, Yan C, Zhao B, Zhao Y, et al. (2023) Polysaccharide-Based Stimulus-Responsive Nanomedicines for Combination Cancer Immunotherapy. Small 19(23).

58. Shah S, Famta P, Tiwari V, Kotha AK, Kashikar R, et al. (2023) Instigation of the epoch of nano vaccines in cancer immunotherapy. Wiley Interdiscip Rev Nanomed Nanobiotechnol 15(3).

59. Bahreyni A, Mohamud Y, Luo H (2020) Emerging nanomedicines for effective breast cancer immunotherapy. J Nanobiotechnology 18(1): 180.

60. Yang Y, Zhao T, Chen Q, Li Y, Xiao Z, et al. (2022) Nanomedicine Strategies for Heating "Cold" Ovarian Cancer (OC): Next Evolution in Immunotherapy of OC. Adv Sci (Weinh) 9(28).

61. Gao S, Yang X, Xu J, Qiu N, Zhai G (2021) Nanotechnology for Boosting Cancer Immunotherapy and Remodeling Tumor Microenvironment: The Horizons in Cancer Treatment. ACS Nano 15(8): 12567-12603.

62. Ahmad W, Sajjad W, Zhou Q, Ge Z (2024) Nanomedicine for combination of chemodynamic therapy and immunotherapy of cancers. Biomater Sci 12(18): 4607-4629.

63. Jiang X, Wu L, Zhang M, Zhang T, Chen C, et al. (2023) Biomembrane nanostructures: Multifunctional platform to enhance tumor chemoimmunotherapy via effective drug delivery. J Control Release 361: 510-533.

64. Liu J, Bai Y, Li Y, Li X, Luo K (2024) Reprogramming the immunosuppressive tumor microenvironment through nanomedicine: an immunometabolism perspective. EBioMedicine 107: 105301.

65. Fuchs N, Meta M, Schuppan D, Nuhn L, Schirmeister T (2020) Novel Opportunities for Cathepsin S Inhibitors in Cancer Immunotherapy by Nanocarrier-Mediated Delivery. Cells 9(9): 2021.

66. Mukherjee S, Sonanini D, Maurer A, Daldrup Link HE (2019) The yin and yang of imaging tumor associated macrophages with PET and MRI. Theranostics 9(25): 7730-7748.

67. Pan X, Han T, Zhao Z, Wang X, Fang X (2024) Emerging Nanotechnology in Preclinical Pancreatic Cancer Immunotherapy: Driving Towards Clinical Applications. Int J Nanomedicine 19: 6619-6641.

68. Ren SN, Zhang ZY, Guo RJ, Wang DR, Chen FF, et al. (2023) Application of nanotechnology in reversing therapeutic resistance and controlling metastasis of colorectal cancer. World J Gastroenterol 29(13): 1911-1941.

69. Cheng Z, Fobian SF, Gurrieri E, Amin M, D'Agostino VG, et al. (2024) Lipid-based nanosystems: the next generation of cancer immune therapy. J Hematol Oncol 17(1): 53.

70. Pi YN, Qi WC, Xia BR, Lou G, Jin WL (2021) Long non-coding RNAs in the Tumor Immune Microenvironment: Biological Properties and Therapeutic Potential. Front Immunol 12: 697083.

71. Pisani P, Airoldi M, Allais A, Aluffi Valletti P, Battista M, et al. (2020) Metastatic disease in head & neck oncology. Acta Otorhinolaryngol Ital 40(SUPPL. 1).

72. Zhang Y, Chen X, Hu B, Zou B, Xu Y (2024) Advancements in nanomedicine delivery systems: unraveling immune regulation strategies for tumor immunotherapy. Nanomedicine (Lond) 19(21-22): 1821-1840.

73. Zhao Y, Zhang X, An M, Zhang J, Liu Y (2023) Recent advancements in nanomedicine-based lipid metabolism for tumour immunotherapy. J Drug Target 31(10): 1050-1064.

74. Ma Y, Shen Y, Zhu B, Li D, Liu J (2020) Application of nanotechnology in circumventing immunotolerance. Pharmazie 75(10): 470-477.

75. Saeed M, Chen F, Ye J, Shi Y, Lammers T, et al. (2021) From Design to Clinic: Engineered Nanobiomaterials for Immune Normalization Therapy of Cancer. Adv Mater 33(30).

76. Elzoghby AO, Ferrone CR, Ferrone S, Nasr ML (2023) Engineered nanomedicines to overcome resistance of pancreatic cancer to immunotherapy. Drug Discov Today 28(1): 103434.

77. Abdelgalil RM, Elmorshedy YM, Elkhodairy KA, Teleb M, Bekhit AA, et al. (2022) Engineered nanomedicines for augmenting the efficacy of colorectal cancer immunotherapy. Nanomedicine (Lond) 17(22): 1721-1745.

78. Lim S, Park J, Shim MK, Um W, Yoon HY, et al. (2019) Recent advances and challenges of repurposing nanoparticle-based drug delivery systems to enhance cancer immunotherapy. Theranostics 9(25): 7906-7923.

79. Azizian K, Pustokhina I, Ghanavati R, Hamblin MR, Amini A, et al. (2021) The potential use of theranostic bacteria in cancer. J Cell Physiol 236(6): 4184-4194.

80. Dogheim GM, El Feel NE, Abd El-Maksod EA, Amer SS, El-Gizawy SA, et al. (2024) Nanomedicines as enhancers of tumor immunogenicity to augment cancer immunotherapy. Drug Discov Today 29(3): 103905.

81. Silveira MJ, Castro F, Oliveira MJ, Sarmento B (2021) Immunomodulatory nanomedicine for colorectal cancer treatment: a landscape to be explored? Biomater Sci 9(9): 3228-3243.

82. Yin L, Li H, Shi L, Chen K, Pan H, et al. (2023) Research advances in nanomedicine applied to the systemic treatment of colorectal cancer. Int J Cancer 152(5): 807-821.

83. Shen F, Fang Y, Wu Y, Zhou M, Shen J, et al. (2023) Metal ions and nanometallic materials in antitumor immunity: Function, application, and perspective. J Nanobiotechnology 21(1): 20.

84. Sofias AM, Combes F, Koschmieder S, Storm G, Lammers T (2021) A paradigm shift in cancer nanomedicine: from traditional tumor targeting to leveraging the immune system. Drug Discov Today 26(6): 1482-1489.

85. Zhang Y, Guoqiang L, Sun M, Lu X (2020) Targeting and exploitation of tumor-associated neutrophils to enhance immunotherapy and drug delivery for cancer treatment. Cancer Biol Med 17(1): 32-43.

86. Thiruppathi J, Vijayan V, Park IK, Lee SE, Rhee JH (2024) Enhancing cancer immunotherapy with photodynamic therapy and nanoparticle: making tumor microenvironment hotter to make immunotherapeutic work better. Front Immunol 15: 1375767.

87. Yang C, Li Y, Yang Y, Chen Z (2020) Overview of Strategies to Improve Therapy against Tumors Using Natural Killer Cell. J Immunol Res 2020: 8459496.

88. Chen Z, Yue Z, Yang K, Shen C, Cheng Z, et al. (2023) Four Ounces Can Move a Thousand Pounds: The Enormous Value of Nanomaterials in Tumor Immunotherapy. Adv Healthc Mater 12(26).

89. Afolabi LO, Adeshakin AO, Sani MM, Bi J, Wan X (2019) Genetic reprogramming for NK cell cancer immunotherapy with CRISPR/Cas9. Immunology 158(2): 63-69.

90. Hao J, Zhao X, Wang C, Cao X, Liu Y (2024) Recent Advances in Nanoimmunotherapy by Modulating Tumor-Associated Macrophages for Cancer Therapy. Bioconjug Chem 35(7): 867-882.

91. Jasim SA, Farber IM, Noraldeen SAM, Bansal P, Alsaab HO, Abdullaev B, et al. (2024) Incorporation of immunotherapies and nanomedicine to better normalize angiogenesis-based cancer treatment. Microvasc Res 154: 104691.

92. Wei Y, Weng X, Wang Y, Yang W (2024) Stimuli-Responsive Polymersomes: Reshaping the Immunosuppressive Tumor Microenvironment. Biomacromolecules 25(8): 4663-4676.

93. Gao J, Wang WQ, Pei Q, Lord MS, Yu HJ (2020) Engineering nanomedicines through boosting immunogenic cell death for improved cancer immunotherapy. Acta Pharmacol Sin 41(7): 986-994.

94. Kim J, Hong J, Lee J, Fakhraei Lahiji S, Kim YH (2021) Recent advances in tumor microenvironment-targeted nanomedicine delivery approaches to overcome limitations of immune checkpoint blockade-based immunotherapy. J Control Release 332: 109-126.

95. Kyu Shim M, Yang S, Sun IC, Kim K (2022) Tumor-activated carrier-free prodrug nanoparticles for targeted cancer Immunotherapy: Preclinical evidence for safe and effective drug delivery. Adv Drug Deliv Rev 183: 114177.

96. Santoni M, Massari F, Montironi R, Battelli N (2021) Manipulating macrophage polarization in cancer patients: From nanoparticles to human chimeric antigen receptor macrophages. Biochim Biophys Acta Rev Cancer 1876(1): 188547.

97. Ma Y, Yi J, Ruan J, Ma J, Yang Q, et al. (2024) Engineered Cell Membrane-Coated Nanoparticles: New Strategies in Glioma Targeted Therapy and Immune Modulation. Adv Healthc Mater 13(20).

98. Cho H, Kim K (2024) Multi-functional nanomedicines for combinational cancer immunotherapy that transform cold tumors to hot tumors. Expert Opin Drug Deliv 21(4): 627-638.

99. Guan M, Liu S, Yang YG, Song Y, Zhang Y, et al. (2024) Chemokine systems in oncology: From microenvironment modulation to nanocarrier innovations. Int J Biol Macromol 268(Pt 1): 131679.

100. Yin Z, Fan J, Xu J, Wu F, Li Y, et al. (2020) Immunoregulatory Roles of Extracellular Vesicles and Associated Therapeutic Applications in Lung Cancer. Front Immunol 11: 2024.

101. Kaur S, Saini AK, Tuli HS, Garg N, Joshi H, et al. (2024) Polymer-mediated nanoformulations: a promising strategy for cancer immunotherapy. Naunyn Schmiedebergs Arch Pharmacol 397(3): 1311-1326.

102. Zhong Z, Deng W, Wu J, Shang H, Tong Y, et al. (2024) Cell membrane coated nanoparticles as a biomimetic drug delivery platform for enhancing cancer immunotherapy. Nanoscale 16(18): 8708-8738.

103. Jiang Z, Fang Z, Hong D, Wang X (2024) Cancer Immunotherapy with "Vascular-Immune" Crosstalk as Entry Point: Associated Mechanisms, Therapeutic Drugs and Nano-Delivery Systems. Int J Nanomedicine 19:7383-7398.

104. Wu X, Li Y, Wen M, Xie Y, Zeng K, et al. (2024) Nanocatalysts for modulating antitumor immunity: fabrication, mechanisms and applications. Chem Soc Rev 53(5): 2643-2692.

105. Lan H, Zhang W, Jin K, Liu Y, Wang Z (2020) Modulating barriers of tumor microenvironment through nanocarrier systems for improved cancer immunotherapy: a review of current status and future perspective. Drug Deliv 27(1): 1248-1262.

106. Hussain Z, Rahim MA, Jan N, Shah H, Rawas Qalaji M, et al. (2021) Cell membrane cloaked nanomedicines for bio-imaging and immunotherapy of cancer: Improved pharmacokinetics, cell internalization and anticancer efficacy. J Control Release 335: 130-157.

107. Choi JU, Park IK, Lee YK, Hwang SR (2020) The Biological Function and Therapeutic Potential of Exosomes in Cancer: Exosomes as Efficient Nanocommunicators for Cancer Therapy. Int J Mol Sci 21(19): 7363.

108. Huang X, Zhang W (2024) Overcoming T Cell Exhaustion in Tumor Microenvironment via Immune Checkpoint Modulation with Nano-Delivery Systems for Enhanced Immunotherapy. Small Methods 8(8).

109. Yu S, Tong L, Shen J, Li C, Hu Y, et al. (2024) Recent research progress based on ferroptosis-related signaling pathways and the tumor microenvironment on it effects. Eur J Med Chem 269: 116290.

110. Dai Z, Wang L, Wang Z (2021) Functional Immunostimulating DNA Materials: The Rising Stars for Cancer Immunotherapy. Macromol Biosci 21(6): e2100083.

111. Yang T, Liu Z, Zhang T, Liu Y (2024) Hybrid nano-stimulator for specific amplification of oxidative stress and precise tumour treatment. J Drug Target 32(7): 756-769.

112. Ku KS, Tang J, Chen Y, Shi Y (2024) Current Advancements in Anti-Cancer Chimeric Antigen Receptor T Cell Immunotherapy and How Nanotechnology May Change the Game. Int J Mol Sci 25(10): 5361.