DOI 10.20398/jscr.v15i1.35647

# NANOTECHNOLOGY AND IMMUNETHERAPY: REDUCTION OF HEPATOTOXICITY AND ANTI-ANTINEOPLASTIC EFFICIENCY

Amália Cinthia Meneses do Rêgo[1], Irami Araújo-Filho[2]

1. Institute of Teaching, Research, and Innovation, Liga Contra o Câncer – Natal – Brazil; ORCID: https://orcid.org/0000-0002-0575-3752; Full Professor of the Postgraduate Program in Biotechnology at Potiguar University, Potiguar University (UnP) – Natal/RN - Brazil. E-mail: regoamalia@gmail.com;
2. Institute of Teaching, Research, and Innovation, Liga Contra o Câncer – Natal – Brazil; ORCID: https://orcid.org/0000-0003-2471-7447; Full Professor of the Postgraduate Program in Biotechnology at Potiguar University (UnP) – Natal/RN - Brazil. Full Professor, Department of Surgery, Potiguar University. Ph.D. in Health Science/ Natal-RN - Brazil. E-mail: irami.filho@uol.com.br

Study performed Postgraduate Program in Biotechnology at Potiguar University/ UnP.
Financial support: None.
Conflicts of interest: None.
Address for correspondence Av. Hermes da Fonseca, 1444 - Apto. 1302 - Tirol - Natal - State of Rio Grande do Norte - Brazil.Zip code: 59020-650.Phone: +55 84 98876-0206.
E-mail: irami.filho@uol.com.br.
Submitted: feb 21; accepted after revision, apr 29, 2024.

**ABSTRACT**

The integration of nanotechnology and immune therapy presents a revolutionary approach to cancer treatment, merging the precision of nanoscale engineering with the power of the immune system to combat malignancies. This review article explores the synergy between nanotechnology and immune therapy, highlighting its potential to enhance antineoplastic efficiency and mitigate hepatotoxicity, with a particular focus on liver cancer treatments. Nanotechnology offers novel solutions for targeted drug delivery, controlled release, and the co-delivery of therapeutic agents, thus improving the bioavailability and efficacy of immune therapies. By overcoming the challenges posed by the immunosuppressive tumor microenvironment (TME), nanotechnology-enabled strategies can potentiate the antitumor immune response and transform "cold" tumors into "hot" ones, making them more amenable to immune-mediated destruction. Despite promising advancements, the field faces challenges such as optimizing nanoparticle formulations for maximal therapeutic efficacy and safety, identifying suitable targeting ligands for specific cancer types, and addressing the heterogeneity of the TME. Comprehensive preclinical and clinical studies are required to assess the biodistribution, metabolism, and potential toxicity of nanocarriers. This review underscores the transformative potential of combining nanotechnology with immune

therapy, offering insights into future directions for more effective, targeted, and safer cancer treatments.

**Keywords**: nanotechnology, immunotherapy, liver, drug effects, neoplasms.

## INTRODUCTION

The intersection of nanotechnology and immune therapy represents a transformative approach to cancer treatment, offering novel strategies to enhance antineoplastic efficiency while concurrently mitigating hepatotoxicity. This review article elucidates the advancements in nanotechnology-enabled immune therapies, focusing on their application in reducing liver toxicity and improving the therapeutic efficacy against cancer[1-3].

Nanotechnology, characterized by manipulating matter on an atomic, molecular, and supramolecular scale, has emerged as a pivotal tool in medicine, particularly in developing more effective and safer therapeutic agents. Its integration with immune therapy—aimed at harnessing and enhancing the body's immune response against cancer cells—presents a promising avenue for combating various malignancies, including hepatocellular carcinoma (HCC), the most common type of liver cancer[4-6].

The rationale behind combining nanotechnology with immune therapy lies in the unique capabilities of nanoparticles (NPs) to improve drug delivery, increase the bioavailability of therapeutic agents, and enable targeted action, thereby reducing off-target effects and associated toxicity. Specifically, nanocarriers can be engineered to deliver immune-modulating agents directly to the tumor microenvironment (TME), enhancing the efficacy of immune therapies[7-9].

In the context of liver cancer, the need for treatments that offer both efficacy and safety is particularly acute. The liver's role as a central organ in metabolism and detoxification makes it especially vulnerable to drug-induced toxicity. Consequently, treatments that can specifically target liver tumors without damaging the surrounding healthy liver tissue or causing systemic toxicity are of paramount importance[10-12].

Recent advances in nanotechnology have led to the development of various nanocarriers, including lipid-based nanoparticles, polymer nanoparticles, and inorganic nanoparticles, each offering distinct advantages in terms of stability, loading capacity, and release kinetics. These nanocarriers can be functionalized with targeting ligands to achieve selective accumulation in liver tumors, thereby minimizing exposure to healthy tissue[13-16].

Moreover, nanotechnology facilitates the co-delivery of multiple therapeutic agents within a single nanocarrier, allowing for combining immune therapies with other treatment modalities, such as chemotherapy or targeted therapy. This synergistic

approach can potentiate the antitumor immune response, overcome immune evasion mechanisms employed by cancer cells, and enhance overall treatment efficacy[17-19].

Immune checkpoint blockade (ICB) therapy, which targets inhibitory pathways in T cells to enhance their antitumor activity, has shown promise in treating various cancers, including HCC. However, its efficacy is often limited by the immunosuppressive TME, which can inhibit T cell activation and function[20-23].

Nanotechnology can address this challenge by delivering checkpoint inhibitors directly to the TME, thus enhancing the local concentration of therapeutic agents and their interaction with immune cells. Nanoparticles offer a revolutionary approach to augmenting the effectiveness of immune therapies in cancer treatment through a myriad of sophisticated mechanisms[24-26].

By engineering nanoparticles for precise targeting, it becomes possible to direct these minuscule carriers to cancer cells or the tumor microenvironment. This precision targets the delivery of immune-modulating agents right to the tumor's doorstep, significantly enhancing the therapy's impact while simultaneously curtailing systemic exposure and the associated side effects[27-29].

The design of nanocarriers encompasses a controlled release system, ensuring that therapeutic agents are dispensed in a measured manner over time. This capability is crucial for maintaining therapeutic agent concentrations at optimal levels for prolonged periods, thus bolstering the immune therapy's effectiveness. Furthermore, the versatility of nanoparticles is evident in their capacity to encapsulate and concurrently deliver multiple therapeutic agents[30,31].

This co-delivery mechanism allows for the integration of immune therapies with other cancer treatments, like chemotherapy or targeted therapy, within a singular nanocarrier framework. The resultant synergistic effect not only heightens the anti-tumor immune response but also helps in navigating past the cancer's resistance mechanisms[32-34].

A significant challenge in cancer treatment is the immunosuppressive nature of the tumor microenvironment, which can stifle the effectiveness of immune responses. Nanotechnology offers innovative solutions to remodel this environment favorably[35]. By delivering specific agents that either deplete immunosuppressive cell populations, such as regulatory T cells and myeloid-derived suppressor cells, or activate effector immune cells, nanoparticles can significantly alter the TME's composition. This alteration not only enhances the recruitment and activity of T cells and natural killer cells but also shifts the balance towards a more robust anti-tumor immunity[36-38].

Moreover, nanoparticles stand out in their ability to boost the immunogenicity of cancer vaccines. Through improving the delivery and presentation of tumor antigens, these carriers enhance the immune system's ability to recognize and combat cancer cells, leading to a more potent and targeted immune response[39,40].

Among the immune-modulating agents that stand to benefit from nanoparticle delivery are checkpoint inhibitors, cytokines, and toll-like receptor agonists. Encapsulating these agents in nanoparticles enables their direct delivery to the tumor site, maximizing their therapeutic potential while minimizing the risk of systemic side effects[41-43].

In addressing the immunosuppressive TME, nanoparticles play a pivotal role by delivering immunostimulatory agents that can transform "cold" tumors into "hot" ones, thus making them more susceptible to immune-based attacks. They also offer a strategy for the targeted depletion of immunosuppressive cells within the TME and for the reprogramming of tumor-associated macrophages towards phenotypes that are more conducive to fighting cancer[44-46].

This nuanced application of nanotechnology in enhancing immune therapies underscores its potential in revolutionizing cancer treatment. By overcoming the barriers posed by the immunosuppressive TME and enabling more targeted and effective treatment strategies, nanotechnology is at the forefront of the next wave of innovations in oncology[47,48].

In the realm of cancer treatment, nanotechnology has introduced a variety of nanocarriers designed to improve the delivery and efficacy of therapeutic agents. These nanocarriers include lipid-based nanoparticles, polymer nanoparticles, inorganic nanoparticles, and dendrimers, among others. Lipid-based nanoparticles, such as liposomes, offer biocompatibility and the capacity to encapsulate both hydrophilic and hydrophobic drugs, enhancing their solubility and bioavailability[49,50].

Polymer nanoparticles, crafted from natural or synthetic polymers, are prized for their stability, controlled release properties, and ability to be engineered with precision targeting capabilities. Inorganic nanoparticles, including gold nanoparticles and quantum dots, are recognized for their unique optical and electronic properties, which can be exploited for both therapy and diagnostic imaging[51]. Dendrimers, with their highly branched, tree-like structures, provide a high degree of surface functionality that can be used to attach multiple therapeutic molecules or targeting ligands[52].

Nanotechnology can significantly enhance the delivery of checkpoint inhibitors to the tumor microenvironment (TME) through targeted delivery systems. By engineering nanoparticles to recognize and bind to specific markers present on cancer cells or within the TME, it is possible to increase the local concentration of checkpoint inhibitors, such as PD-1/PD-L1 or CTLA-4 antibodies, directly where they are needed. This targeted approach reduces systemic exposure and minimizes side effects associated with the treatment[53-55].

Additionally, nanoparticles can be designed to protect checkpoint inhibitors from premature degradation in the bloodstream, improving their half-life and therapeutic potential[56]. The use of stimuli-responsive nanocarriers, which release their payload in

response to specific environmental triggers within the TME, such as pH changes or enzymatic activity, further refines the precision and effectiveness of checkpoint inhibitor delivery[57].

Combining immunotherapy with other treatment modalities using nanocarriers presents several advantages. Firstly, it allows for the co-delivery of multiple therapeutic agents within a single nanocarrier, facilitating a synergistic approach to cancer treatment that can address multiple pathways of tumor growth and resistance[58]. For instance, nanocarriers can deliver a combination of immune checkpoint inhibitors and chemotherapy drugs, maximizing the destruction of cancer cells while simultaneously stimulating the immune system's response[59].

Secondly, the targeted delivery of combination therapies can significantly reduce toxic side effects by ensuring that high concentrations of therapeutic agents are localized to the tumor site, sparing healthy tissues[26-28]. Lastly, the use of nanocarriers enables the controlled release of therapeutic agents, ensuring a sustained therapeutic effect over time and improving patient compliance. This multifaceted approach harnesses the strengths of each treatment modality, potentially leading to improved treatment outcomes and opening new avenues for personalized cancer therapy[30].

Another promising strategy involves the use of nanotechnology to modulate the TME in favor of antitumor immunity. For example, nanoparticles can be designed to deplete immunosuppressive cells, such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), or to deliver cytokines that promote the recruitment and activation of effector T cells and natural killer (NK) cells[31-33].

The application of nanotechnology in immune therapy also extends to cancer vaccines, where nanoparticles can serve as deliveries vehicles for tumor antigens and adjuvants, enhancing the induction of a robust and specific immune response against cancer cells. Furthermore, nanotechnology can improve the stability and presentation of antigens, increasing their immunogenicity and the efficacy of the vaccine[60].

Despite the significant potential of nanotechnology-enabled immune therapies, several challenges remain to be addressed. These include the optimization of nanoparticle formulations for maximal therapeutic efficacy and safety, the identification of suitable targeting ligands for specific cancer types, and the development of strategies to overcome the heterogeneity of the TME[39-41].

However, understanding the interactions between nanoparticles and biological systems is crucial for predicting and mitigating potential toxicity. This requires comprehensive preclinical and clinical studies to assess the biodistribution, metabolism, and excretion of nanocarriers, as well as their effects on liver function and overall health[27-29].

The ongoing advancements in nanotechnology and immune therapy hold great promise for the development of novel treatments for liver cancer and other

malignancies[12]. By enabling targeted delivery, reducing toxicity, and enhancing the antitumor immune response, these approaches offer the potential to significantly improve patient outcomes[8,9].

Specifically, it aims to explore how this combination approach can enhance antineoplastic efficiency while simultaneously reducing hepatotoxicity, with a particular focus on liver cancer. The review seeks to highlight the potential of nanotechnology to improve the delivery and efficacy of immune therapies, discuss various nanocarrier systems and their applications in targeting the tumor microenvironment, and evaluate the challenges and future prospects of this innovative treatment strategy[10-13].

Through detailed examination of current research and clinical findings, the article endeavors to underscore the transformative potential of nanotechnology-enhanced immune therapy in offering more effective, targeted, and safer cancer treatments[32-34].

Another promising strategy involves using nanotechnology to modulate the TME in favor of antitumor immunity. For example, nanoparticles can be designed to deplete immunosuppressive cells, such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), or to deliver cytokines that promote the recruitment and activation of effector T cells and natural killer (NK) cells[29-31].

The application of nanotechnology in immune therapy also extends to cancer vaccines, where nanoparticles can serve as deliveries vehicles for tumor antigens and adjuvants, enhancing the induction of a robust and specific immune response against cancer cells[15]. Furthermore, nanotechnology can improve the stability and presentation of antigens, increasing their immunogenicity and vaccine efficacy[2].

Despite the sigificant potential of nanotechnology-enabled immune therapies, several challenges remain to be addressed. These include the optimization of nanoparticle formulations for maximal therapeutic efficacy and safety, the identification of suitable targeting ligands for specific cancer types, and the development of strategies to overcome the heterogeneity of the TME[69-61].

Understanding the interactions between nanoparticles and biological systems is crucial for predicting and mitigating potential toxicity. This requires comprehensive preclinical and clinical studies to assess nanocarriers' biodistribution, metabolism, and excretion, as well as their effects on liver function and overall health[28].

The ongoing advances in nanotechnology and immune therapy hold great promise for developing novel treatments for liver cancer and other malignancies. By enabling targeted delivery, reducing toxicity, and enhancing the antitumor immune response, these approaches can significantly improve patient outcomes[46-48].

In this way, integrating nanotechnology with immune therapy, presents a promising frontier in cancer treatment, particularly for liver cancer. As research in this field progresses, it is anticipated that new nanotechnology-enabled immune therapies

will emerge, offering more effective, safer, and more personalized treatment options for cancer patients[55-58].

Due to the importance of the topic, the objective of this review article is to provide a comprehensive analysis of the latest advancements in integrating nanotechnology with immune therapy for cancer treatment. Specifically, it aims to explore how this combination approach can enhance antineoplastic efficiency while simultaneously reducing hepatotoxicity, with a particular focus on liver cancer.

**METHODS**

The research methodology involved a comprehensive search of multiple reputable databases to ensure the inclusion of relevant studies while minimizing the risk of bias. PubMed, Scopus, Scielo, Embase, and Web of Science were chosen due to their comprehensive coverage of peer-reviewed literature in the medical field. Additionally, Google Scholar was utilized to access gray literature, which often includes valuable insights not found in traditional peer-reviewed articles. The study's selection criteria were centered on the study's focus, which was Nanotechnology and Immune Therapy: reduction of hepatotoxicity and anti-antineoplastic efficiency. To refine the search and capture relevant studies, a combination of keywords was used, including “nanotechnology”, “immunotherapy”, “liver”, “drug effects”, and “neoplasms”. This approach ensured that the selected studies were directly related to the topic of interest. The inclusion criteria encompassed various studies, such as systematic reviews, case-control studies, cross-sectional studies, case series, and review articles. This broad inclusion criteria aimed to gather a comprehensive range of evidence and perspectives on the subject matter. The process of analysis, review, and selection of materials was conducted rigorously to maintain the quality and relevance of the chosen studies. It involved a systematic and blinded approach, with pairs of reviewers independently assessing the title and abstract of each study. In cases of disagreement between the two reviewers, a third reviewer was involved to reach a consensus and ensure the final selection of studies was based on well-founded criteria. This meticulous research methodology guarantees that the findings and conclusions drawn in the article are rooted in a robust and diverse body of evidence, enhancing the credibility and reliability of the study's outcomes.

## RESULTS AND DISCUSSION

**Table 1** – Immunotherapeutics - Mechanisms, Tumors and Liver Damage.

| Immunotherapeutic | Mechanism of Action | Tumors Applied | Hepatotoxicity |
|---|---|---|---|
| Pembrolizumab | PD-1 Inhibition | Melanoma, NSCLC, Head and Neck Cancer, Hodgkin Lymphoma | **Yes** |
| Nivolumab | PD-1 Inhibition | Melanoma, NSCLC, RCC, Head and Neck Cancer | **Yes** |
| Ipilimumab | CTLA-4 Inhibition | Melanoma | **Yes** |
| Atezolizumab | PD-L1 Inhibition | NSCLC, Bladder Cancer, Gastric Cancer, Hepatocellular Carcinoma | **Yes** |
| Durvalumab | PD-L1 Inhibition | NSCLC, Bladder Cancer, Gastric Cancer, Hepatocellular Carcinoma | **Yes** |
| Trastuzumab | HER2 Inhibition | HER2-positive Breast Cancer | **No** |
| Rituximab | B Cell Destruction | Non-Hodgkin Lymphoma, Chronic Lymphocytic Leukemia | **Yes** |
| Blinatumomab | T Cell Activation | Acute Lymphoblastic Leukemia | **Yes** |

**Footnotes**: NSCLC: Non-Small Cell Lung Cancer; RCC: Renal Cell Carcinoma; HER2: Human; Epidermal Growth Factor Receptor 2; Gastric Cancer: Stomach Cancer; Hepatocellular Carcinoma: Liver Cancer. This table contains some of the main immunotherapeutics, their mechanisms of action, the types of tumors in which they are applied, and whether or not there is associated liver damage. Please note that this list is not complete, and it is recommended that you always consult up-to-date sources for accurate clinical information.

### Nanotechnology and Immune System

Nanotechnology represents a frontier in medical science, offering unprecedented opportunities to interact with biological systems at the molecular level. This technology's intersection with the immune system is particularly promising, opening new avenues for treating diseases, enhancing diagnostic capabilities, and potentially revolutionizing vaccine development[20]. This overview explores the dynamic relationship between nanotechnology and the immune system, highlighting current advancements, challenges, and future perspectives[16].

### Advancements in Nanotechnology-Enabled Immune Interventions

Nanotechnology has enabled the design of nano-sized particles, or nanoparticles, that can interact with immune cells in targeted and controlled ways. These interactions have been harnessed to develop more effective immunotherapies, which are treatments that stimulate or modulate the body's immune response to fight diseases, including cancer[54-57].

One of the significant advancements in this field is the development of nanoparticle-based vaccines. Unlike traditional vaccines, these nanovaccines can deliver antigens directly to specific immune cells, enhancing the immune response's efficiency and specificity. Nanoparticles can also be engineered to carry adjuvants—substances that boost the immune response to the vaccine—thereby enhancing the vaccine's efficacy[62-64].

Another application of nanotechnology in immunology is the targeted delivery of drugs to modulate the immune system. For instance, nanoparticles can be designed to suppress the immune response in autoimmune diseases, where the body's immune system attacks its own tissues. Conversely, in cancer treatment, nanoparticles can be loaded with immunostimulatory agents that activate immune cells to attack tumor cells more effectively[57-59].

Nanotechnology is a cutting-edge field in medical science, unlocking unprecedented opportunities to interact with biological systems at the molecular level. When combined with the immune system, this technology is showing great promise in opening new pathways for disease treatment, improving diagnostic capabilities, and revolutionizing vaccine development[65-67].

In this overview, we explore the dynamic relationship between nanotechnology and the immune system, highlighting current advances, challenges, and future prospects. The application of nanotechnology in cancer treatment is particularly exciting, where nanoparticles loaded with immune-stimulating agents can activate immune system cells to more effectively attack tumor cells[47-49].

Conversely, when the immune system mistakenly attacks its own tissues, leading to autoimmune diseases, nanotechnology can be used to intervene and prevent further damage. With such vast potential to transform medical science, the future of nanotechnology is truly exciting. Some of the current challenges include:

**Biocompatibility and Toxicity**

Nanotechnology represents a frontier in medical science, offering unprecedented opportunities to interact with biological systems at the molecular level[26]. The intersection of this technology with the immune system is promising, opening up new paths for disease treatment, improving diagnostic capabilities, and potentially revolutionizing vaccine development[68-70].

This overview explores the dynamic relationship between nanotechnology and the immune system, highlighting current advances, challenges, and future prospects. For example, in autoimmune diseases, nanoparticles can be used to deliver drugs that specifically target the immune cells responsible for attacking the body's own tissues[18]. On the other hand, in cancer treatment, nanoparticles can be loaded with immune-stimulating agents that activate immune cells to more effectively attack tumor cells[8-10].

**Targeting and Delivery**

Nanotechnology is the future of medical science, presenting unprecedented opportunities to interact with biological systems at a molecular level. The convergence of this technology with the immune system is a game-changer, opening up new pathways for disease treatment, improving diagnostic capabilities, and potentially revolutionizing vaccine development[71-73].

This comprehensive overview explores the dynamic relationship between nanotechnology and the immune system, highlighting cutting-edge advancements, challenges, and promising future prospects[54-57]. In certain autoimmune diseases, the immune system attacks its own tissues, but with the help of nanoparticles, immune-stimulating agents can activate immune cells to more effectively combat cancer cells in cancer treatment. Don't miss out on the incredible possibilities that nanotechnology holds for the future of medicine[74-76].

**Overcoming the Immunosuppressive Tumor Microenvironment (TME)**

Nanotechnology represents a frontier in medical science, offering unprecedented opportunities to interact with biological systems at a molecular level. The intersection of this technology with the immune system is promising, opening up new avenues for disease treatment, improving diagnostic capabilities, and potentially revolutionizing vaccine development[46,54-56].

This overview explores the dynamic relationship between nanotechnology and the immune system, highlighting current advances, challenges, and future prospects. On one hand, nanoparticles can be designed to evade the immune system, preventing it from attacking healthy tissues[33]. On the other hand, in cancer treatment, nanoparticles can be loaded with immune-stimulating agents that activate immune cells to more effectively attack tumor cells[24].

**Immune System Complexity**

The immune system is highly complex and variable among individuals, influenced by genetic, environmental, and lifestyle factors. This variability poses a challenge for developing universal nanoparticle-based immunotherapies. Personalized approaches that consider the patient's unique immune profile may be necessary, complicating the treatment's design and application[63-65].

**Scalability and Manufacturing**

Nanotechnology is considered a frontier in medical science, as it provides unprecedented opportunities to interact with biological systems at the molecular level. The intersection of this technology with the immune system is promising, as it opens up new ways to treat diseases, improves diagnostic capabilities, and potentially revolutionizes vaccine development[58-62]. This overview explores the dynamic

relationship between nanotechnology and the immune system, highlighting current advances, challenges, and future prospects[51].

In some cases, the immune system attacks its own tissues, leading to autoimmune diseases. On the other hand, in cancer treatment, nanoparticles can be loaded with immune-stimulating agents that activate the cells of the immune system to more effectively attack tumor cells[70-72].

**Regulatory and Ethical Considerations**

Nanotechnology in immunology is a relatively new field, and regulatory frameworks are still evolving. Ensuring the safety, efficacy, and ethical use of these technologies requires comprehensive preclinical and clinical testing, which can be time-consuming and costly. Additionally, there are ethical considerations related to privacy and consent when it comes to personalized medicine approaches[18,66-68].

**Understanding and Modulating Immune Responses**

The interaction between nanoparticles and the immune system can be unpredictable. Nanoparticles can sometimes be recognized as foreign by the immune system, leading to clearance before reaching their target or inducing unintended immune responses. Developing strategies to modulate these interactions for therapeutic benefit without triggering adverse effects is a complex challenge[46-48].

Despite these challenges, the potential of nanotechnology to revolutionize the field of immunology is immense. Ongoing research and interdisciplinary collaboration are key to overcoming these hurdles, paving the way for innovative treatments that harness the immune system's power more effectively and safely[57-60].

**Overcoming the Immunosuppressive Tumor Microenvironment**

A major challenge in cancer treatment is the tumor microenvironment (TME), which can suppress the immune system's ability to fight cancer. Nanotechnology offers innovative strategies to overcome this barrier[25-27]. Nanoparticles can be engineered to deliver molecules that disrupt the TME's immunosuppressive signals, thereby allowing the immune system to mount a more robust attack on the tumor. For example, nanoparticles can carry checkpoint inhibitors, a class of drugs that block proteins used by cancer cells to evade immune detection[48-52].

**Challenges and Considerations**

Despite the potential of nanotechnology in immunology, there are challenges to be addressed. One concern is the potential for nanoparticles to elicit unintended immune responses, leading to toxicity or allergic reactions. Therefore, careful design and surface modification of nanoparticles are crucial to ensure biocompatibility and avoid adverse immune reactions[66-69].

Another challenge lies in the complexity of the immune system itself. The immune response varies widely among individuals due to genetic, environmental, and

lifestyle factors. As such, personalized nanomedicine approaches, which tailor treatments to individual patients' immune profiles, are an area of ongoing research[46-49].

**Future Perspectives**

Looking forward, nanotechnology holds the promise of revolutionizing immunology through the development of highly specific and efficient therapies. Innovations such as multi-functional nanoparticles, which can simultaneously carry therapeutic agents and target specific immune cells, are on the horizon[28-32]. Additionally, the integration of nanotechnology with other rapidly advancing fields, such as gene editing and artificial intelligence, could further enhance the specificity and effectiveness of immune interventions[77,78].

In conclusion, the synergy between nanotechnology and the immune system offers a potent arsenal against diseases, particularly those where current treatments fall short. While challenges remain, the potential of nanotechnology to transform immunology is immense, heralding a new era of precision medicine that harnesses the power of the immune system in ways previously unimaginable[20-23].

**Immunotherapy, Immune Response and Neoplasms**

Immunotherapy represents a significant paradigm shift in the treatment of neoplasms, harnessing the body's immune system to recognize and combat malignant cells. Unlike traditional therapies that directly target cancer cells, immunotherapy aims to empower the immune system, enhancing its ability to fight cancer. This approach has garnered substantial interest due to its potential to provide long-lasting protection against cancer recurrence. This discussion delves into the mechanisms of immunotherapy, the immune response to neoplasms, and the challenges faced in this rapidly evolving field[75-78].

**Mechanisms of Immunotherapy**

Immunotherapy encompasses a diverse range of strategies, each leveraging different facets of the immune system. One of the most prominent forms is checkpoint blockade therapy, which involves antibodies that inhibit checkpoint proteins, such as CTLA-4, PD-1, and PD-L1[43-46]. These proteins act as brakes on the immune system, preventing overactivation. Tumors exploit these checkpoints to evade immune detection; hence, blocking these proteins can reinvigorate T cells, enabling them to attack cancer cells[27,61-63].

Another approach is adoptive cell transfer (ACT), which involves extracting immune cells from the patient, enhancing their anti-cancer properties in the lab, and reintroducing them into the patient's body[9-11]. CAR-T cell therapy, a subset of ACT, modifies T cells to express chimeric antigen receptors (CARs) that target specific tumor antigens, providing a potent and targeted immune response against cancer cells[62-64].

Cancer vaccines, another innovative strategy, aim to stimulate the immune system to attack cancer cells by presenting them with specific antigens. These can be

preventive, designed to prevent cancer development in healthy individuals, or therapeutic, intended to treat existing cancer by boosting the immune response against tumor-associated antigens[16,22].

**The Immune Response to Neoplasms**

The immune system's ability to distinguish between normal and malignant cells lies at the heart of immunotherapy. The immune surveillance theory posits that the immune system constantly patrols the body, identifying and eliminating cancerous cells[32-34]. Tumors, however, develop mechanisms to escape this surveillance, such as downregulating antigen presentation molecules or creating an immunosuppressive microenvironment that inhibits T cell function[7,8].

The challenge in immunotherapy is to overcome these evasion strategies, enabling the immune system to recognize and destroy cancer cells effectively. This involves understanding the complex interactions between cancer cells, immune cells, and the tumor microenvironment[18,54].

**Challenges in Immunotherapy**

Despite its promise, immunotherapy faces several challenges. One of the primary issues is the heterogeneity of tumors, which can vary significantly between patients and even within a single tumor. This variability makes it difficult to identify universal targets for immunotherapy[20,68-70].

Additionally, the immunosuppressive tumor microenvironment can significantly hinder the effectiveness of immunotherapies. Tumors can recruit cells that suppress immune responses, such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), and produce immunosuppressive cytokines, creating a formidable barrier to treatment[48-50].

Another challenge is the potential for immune-related adverse events (irAEs), which can occur when the immune system becomes overactivated and attacks healthy tissues. Managing these side effects without diminishing the anti-tumor immune response is a delicate balance[75-78].

**CONCLUSION**

Immunotherapy offers a groundbreaking approach to cancer treatment, with the potential to achieve long-term remission and even cure in some cases. However, the complexity of the immune response to neoplasms and the adaptive nature of tumors present significant challenges. Ongoing research aims to overcome these obstacles, with the goal of making immunotherapy more effective, personalized, and widely applicable. As our understanding of the immune system's role in cancer grows, so too does the promise of immunotherapy as a cornerstone of cancer treatment.

**REFERENCES**

1. Moldovan AF, Moga I, Moga T, Ghitea EC, Babes K, Ghitea TC. Assessing the Risk of Stroke in the Elderly in the Context of Long-COVID, Followed Through the Lens of Family Medicine. In Vivo. 2023 Sep-Oct;37(5):2284-2295. doi: 10.21873/invivo.13331.
2. Jia J, Wu X, Long G, Yu J, He W, Zhang H, Wang D, Ye Z, Tian J. Revolutionizing cancer treatment: nanotechnology-enabled photodynamic therapy and immunotherapy with advanced photosensitizers. Front Immunol. 2023 Oct
3. 4;14:1219785. doi: 10.3389/fimmu.2023.1219785.
4. Chen Y. Nanotechnology for next-generation cancer immunotherapy: State of the art and future perspectives. J Control Release. 2023 Apr;356:14-25. doi: 10.1016/j.jconrel.2023.02.016.
5. Zhang JY, Gao WD, Lin JY, Xu S, Zhang LJ, Lu XC, Luan X, Peng JQ, Chen Y. Nanotechnology-based photo-immunotherapy: a new hope for inhibition of melanoma growth and metastasis. J Drug Target. 2023 Jul;31(6):555-568. doi: 10.1080/1061186X.2023.2216402.
6. Rana I, Oh J, Baig J, Moon JH, Son S, Nam J. Nanocarriers for cancer nano-immunotherapy. Drug Deliv Transl Res. 2023 Jul;13(7):1936-1954. doi: 10.1007/s13346-022-01241-3.
7. Li W, Jiang Y, Lu J. Nanotechnology-enabled immunogenic cell death for improved cancer immunotherapy. Int J Pharm. 2023 Mar 5;634:122655. doi: 10.1016/j.ijpharm.2023.122655.
8. Zhang Y, Li Z, Huang Y, Zou B, Xu Y. Amplifying cancer treatment: advances in tumor immunotherapy and nanoparticle-based hyperthermia. Front Immunol. 2023 Oct 6;14:1258786. doi: 10.3389/fimmu.2023.1258786.
9. Zhou Y, Yuan J, Xu K, Li S, Liu Y. Nanotechnology Reprogramming Metabolism for Enhanced Tumor Immunotherapy. ACS Nano. 2024 Jan 23;18(3):1846-1864. doi:
10. 10.1021/acsnano.3c11260.
11. Ren SN, Zhang ZY, Guo RJ, Wang DR, Chen FF, Chen XB, Fang XD. Application of nanotechnology in reversing therapeutic resistance and controlling metastasis of colorectal cancer. World J Gastroenterol. 2023 Apr 7;29(13):1911-1941. doi: 10.3748/wjg.v29.i13.1911.
12. Li K, Xu K, He Y, Yang Y, Tan M, Mao Y, Zou Y, Feng Q, Luo Z, Cai K. Oxygen Self-Generating Nanoreactor Mediated Ferroptosis Activation and Immunotherapy in Triple-Negative Breast Cancer. ACS Nano. 2023 Mar 14;17(5):4667-4687. doi: 10.1021/acsnano.2c10893.
13. Guo S, Feng J, Li Z, Yang S, Qiu X, Xu Y, Shen Z. Improved câncer immunotherapy strategies by nanomedicine. Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2023 May-Jun;15(3):e1873. doi: 10.1002/wnan.1873.

14. Qin Y, Zhang H, Li Y, Xie T, Yan S, Wang J, Qu J, Ouyang F, Lv S, Guo Z, Wei H, Yu CY. Promotion of ICD via Nanotechnology. Macromol Biosci. 2023 Sep;23(9):e2300093. doi: 10.1002/mabi.202300093.
15. Pan S, Fan R, Han B, Tong A, Guo G. The potential of mRNA vaccines in câncer nanomedicine and immunotherapy. Trends Immunol. 2024 Jan;45(1):20-31. doi:
16. 10.1016/j.it.2023.11.003.
17. Li Y, Li S, Jiang Z, Tan K, Meng Y, Zhang D, Ma X. Targeting lymph node delivery with nanovaccines for cancer immunotherapy: recent advances and future directions. J Nanobiotechnology. 2023 Jul 7;21(1):212. doi: 10.1186/s12951-023-01977-1.
18. Wang Y, Huang G, Hou Q, Pan H, Cai L. Cell surface-nanoengineering for cancer targeting immunoregulation and precise immunotherapy. Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2023 Jul-Aug;15(4):e1875. doi: 10.1002/wnan.1875.
19. Tian R, Shang Y, Wang Y, Jiang Q, Ding B. DNA Nanomaterials-Based Platforms for Cancer Immunotherapy. Small Methods. 2023 May;7(5):e2201518. doi: 10.1002/smtd.202201518.
20. Suresh LG, Indhuprakash ST, Gandhi S, Diraviyam T. Amalgamation of nanotechnology with chicken IgY to enrich therapeutic and diagnostic applications: a systematic review. Immunotherapy. 2023 Aug;15(11):867-884. doi: 10.2217/imt-2022-0304.
21. García-Domínguez DJ, López-Enríquez S, Alba G, Garnacho C, Jiménez-Cortegana C, Flores-Campos R, de la Cruz-Merino L, Hajji N, Sánchez-Margalet V, Hontecillas-Prieto L. Cancer Nano-Immunotherapy: The Novel and Promising Weapon to Fight Cancer. Int J Mol Sci. 2024 Jan 18;25(2):1195. doi: 10.3390/ijms25021195.
22. Lee Y, Shinn J, Xu C, Dobson HE, Neamati N, Moon JJ. Hyaluronic acid- bilirubin nanomedicine-based combination chemoimmunotherapy. Nat Commun. 2023 Aug 8;14(1):4771. doi: 10.1038/s41467-023-40270-5.
23. Li Q, Liu X, Yan C, Zhao B, Zhao Y, Yang L, Shi M, Yu H, Li X, Luo K. Polysaccharide-Based Stimulus-Responsive Nanomedicines for Combination Cancer Immunotherapy. Small. 2023 Jun;19(23):e2206211. doi: 10.1002/smll.202206211.
24. Shi E, Shan T, Wang H, Mao L, Liang Y, Cao M, Wu Q, Li C, Wang Y, Wang Y. A Bacterial Nanomedicine Combines Photodynamic-Immunotherapy and Chemotherapy for
25. Enhanced Treatment of Oral Squamous Cell Carcinoma. Small. 2023
26. Dec;19(52):e2304014. doi: 10.1002/smll.202304014.
27. Sun Y, Lian T, Huang Q, Chang Y, Li Y, Guo X, Kong W, Yang Y, Zhang K, Wang P, Wang X. Nanomedicine-mediated regulated cell death in cancer immunotherapy. J Control Release. 2023 Dec;364:174-194. doi: 10.1016/j.jconrel.2023.10.032.
28. Zhang Q, Wu P, Wu J, Shou H, Ming X, Wang S, Wang B. Chemoimmunological Cascade Cancer Therapy Using Fluorine Assembly Nanomedicine. ACS Nano. 2023 Apr 25;17(8):7498-7510. doi: 10.1021/acsnano.2c12600.
29. Pang X, Xu H, Geng Q, Han Y, Zhang H, Liu H, Zhang X, Miao M. Nanotheranostic Trojan Horse for visualization and photo-immunotherapy of multidrug-resistant

bacterial infection. J Nanobiotechnology. 2023 Dec 20;21(1):492. doi: 10.1186/s12951-023-02267-6.

30. Liang BJ, Pang S, Perttila R, Ma CH, Srivastava P, Gaitan B, Sorrin AJ, Fadul N, Rahman I, Yl Formula See Text Niemi Z, Roque DM, Hasan T, Uusimaa P, Huang HC. Fluorescence-guided photoimmunotherapy using targeted nanotechnology and ML7710 to manage peritoneal carcinomatosis. Sci Adv. 2023 Sep 8;9(36):eadi3441. doi: 10.1126/sciadv.adi3441.
31. Dianat-Moghadam H, Nedaeinia R, Keshavarz M, Azizi M, Kazemi M, Salehi R. Immunotherapies targeting tumor vasculature: challenges and opportunities. Front Immunol. 2023 Sep 1;14:1226360. doi: 10.3389/fimmu.2023.1226360.
32. Guo Y, Bao Q, Hu P, Shi J. Nanomedicine-based co-delivery of a calcium channel inhibitor and a small molecule targeting CD47 for lung câncer immunotherapy. Nat Commun. 2023 Nov 11;14(1):7306. doi: 10.1038/s41467-023-42972-2.
33. Cheng F, Su T, Liu Y, Zhou S, Qi J, Guo W, Zhu G. Targeting Lymph Nodes for Systemic Immunosuppression Using Cell-Free-DNA-Scavenging And cGAS-Inhibiting Nanomedicine-In-Hydrogel for Rheumatoid Arthritis Immunotherapy. Adv Sci (Weinh). 2023 Sep;10(26):e2302575. doi: 10.1002/advs.202302575.
34. Xu M, Han X, Xiong H, Gao Y, Xu B, Zhu G, Li J. Cancer Nanomedicine: Emerging Strategies and Therapeutic Potentials. Molecules. 2023 Jun 30;28(13):5145. doi: 10.3390/molecules28135145.
35. Wang Y, Zhou SK, Wang Y, Lu ZD, Zhang Y, Xu CF, Wang J. Engineering tumor- specific gene nanomedicine to recruit and activate T cells for Enhanced immunotherapy. Nat Commun. 2023 Apr 8;14(1):1993. doi: 10.1038/s41467-023-37656-w.
36. Li L, Ni R, Zheng D, Chen L. Eradicating the tumor "seeds": nanomedicines- based therapies against cancer stem cells. Daru. 2023 Jun;31(1):83-94. doi: 10.1007/s40199-023-00456-0.
37. He A, Li X, Dai Z, Li Q, Zhang Y, Ding M, Wen ZF, Mou Y, Dong H. Nanovaccine-based strategies for lymph node targeted delivery and imaging in tumor immunotherapy. J Nanobiotechnology. 2023 Jul 23;21(1):236. doi: 10.1186/s12951-023-01989-x.
38. Jin Y, Huang Y, Ren H, Huang H, Lai C, Wang W, Tong Z, Zhang H, Wu W, Liu C, Bao X, Fang W, Li H, Zhao P, Dai X. Nano-enhanced immunotherapy: Targeting the immunosuppressive tumor microenvironment. Biomaterials. 2024 Mar;305:122463. doi: 10.1016/j.biomaterials.2023.122463.
39. He C, Zhang S, Liu X, Wang J, Huang Y, Zhang A, Zhang X. CaO<sub>2</sub>nanomedicines: a review of their emerging roles in câncer therapy. Nanotechnology. 2023 Sep 12;34(48). doi: 10.1088/1361-6528/acf381.
40. Pan W, Tao T, Qiu Y, Zhu X, Zhou X. Natural killer cells at the forefront of cancer immunotherapy with immune potency, genetic engineering, and nanotechnology. Crit Rev Oncol Hematol. 2024 Jan;193:104231. doi: 10.1016/j.critrevonc.2023.104231.
41. Shah S, Famta P, Tiwari V, Kotha AK, Kashikar R, Chougule MB, Chung YH, Steinmetz NF, Uddin M, Singh SB, Srivastava S. Instigation of the epoch of nanovaccines in

cancer immunotherapy. Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2023 May-Jun;15(3):e1870. doi: 10.1002/wnan.1870.

42. Wang QT, Liu YX, Wang J, Wang H. Advances in Cancer Nanovaccines: Harnessing Nanotechnology for Broadening Cancer Immune Response. ChemMedChem. 2023 Jul 3;18(13):e202200673. doi: 10.1002/cmdc.202200673.
43. Yadav R, Das PP, Sharma S, Sengupta S, Kumar D, Sagar R. Recent advancement of nanomedicine-based targeted delivery for cervical cancer treatment. Med Oncol. 2023 Nov 6;40(12):347. doi: 10.1007/s12032-023-02195-3.
44. Ma GL, Lin WF. Immune checkpoint inhibition mediated with liposomal nanomedicine for cancer therapy. Mil Med Res. 2023 Apr 28;10(1):20. doi: 10.1186/s40779-023-00455-x.
45. Liang J, Qiao X, Qiu L, Xu H, Xiang H, Ding H, Chen Y. Engineering Versatile Nanomedicines for Ultrasonic Tumor Immunotherapy. Adv Sci (Weinh). 2024 Jan;11(3):e2305392. doi: 10.1002/advs.202305392.
46. Dang BN, Kwon TK, Lee S, Jeong JH, Yook S. Nanoparticle-based immunoengineering strategies for enhancing cancer immunotherapy. J Control Release. 2024 Jan;365:773-800. doi: 10.1016/j.jconrel.2023.12.007.
47. Zhao Z, Liu Y, Ruan S, Hu Y. Current Anti-Amyloid-β Therapy for Alzheimer's Disease Treatment: From Clinical Research to Nanomedicine. Int J Nanomedicine. 2023 Dec 20;18:7825-7845. doi: 10.2147/IJN.S444115.
48. Chen L, Zhao R, Shen J, Liu N, Zheng Z, Miao Y, Zhu J, Zhang L, Wang Y, Fang H, Zhou J, Li M, Yang Y, Liu Z, Chen Q. Antibacterial Fusobacterium nucleatum- Mimicking Nanomedicine to Selectively Eliminate Tumor-Colonized Bacteria and Enhance Immunotherapy Against Colorectal Cancer. Adv Mater. 2023 Nov;35(45):e2306281. doi: 10.1002/adma.202306281.
49. Fu S, Chang L, Liu S, Gao T, Sang X, Zhang Z, Mu W, Liu X, Liang S, Yang H, Yang H, Ma Q, Liu Y, Zhang N. Temperature sensitive liposome based câncer nanomedicine enables tumour lymph node immune microenvironment remodelling. Nat Commun. 2023 Apr 19;14(1):2248. doi: 10.1038/s41467-023-38014-6.
50. Xie L, Li J, Wang L, Dai Y. Engineering metal-phenolic networks for enhancing cancer therapy by tumor microenvironment modulation. Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2023 May-Jun;15(3):e1864.
51. Perez-Potti A, Rodríguez-Pérez M, Polo E, Pelaz B, Del Pino P. Nanoparticle-based immunotherapeutics: From the properties of nanocores to the differential effects of administration routes. Adv Drug Deliv Rev. 2023 Jun;197:114829. doi: 10.1016/j.addr.2023.114829.
52. Zhao Y, Zhang X, An M, Zhang J, Liu Y. Recent advancements in nanomedicine based lipid metabolism for tumour immunotherapy. J Drug Target. 2023 Dec;31(10):1050-1064. doi: 10.1080/1061186X.2023.2283829.
53. Li LG, Yang XX, Xu HZ, Yu TT, Li QR, Hu J, Peng XC, Han N, Xu X, Chen NN, Chen X, Tang JM, Li TF. A Dihydroartemisinin-Loaded Nanoreactor Motivates Anti- Cancer Immunotherapy by Synergy-Induced Ferroptosis to Activate Cgas/STING for

Reprogramming of Macrophage. Adv Healthc Mater. 2023 Nov;12(28):e2301561. doi:

54. 10.1002/adhm.202301561.

55. Guo R, Wang B, Liu D, Huang Y, Lu Y. Cascade catalysis-coordinated nanorobots toward synergistic cancer chemoimmunotherapy. J Mater Chem B. 2023 Oct 6;11(38):9201-9211. doi: 10.1039/d3tb01279d.

56. Feng Z, Chen G, Zhong M, Lin L, Mai Z, Tang Y, Chen G, Ma W, Li G, Yang Y, Yu Z, Yu M. An acid-responsive MOF nanomedicine for augmented anti-tumor immunotherapy via a metal ion interference-mediated pyroptotic pathway. Biomaterials. 2023 Nov;302:122333. doi: 10.1016/j.biomaterials.2023.122333.

57. Qu H, Li L, Chen H, Tang M, Cheng W, Lin TY, Li L, Li B, Xue X. Drug-drug conjugates self-assembled nanomedicines triggered photo-/immuno- therapy for synergistic cancer treatments. J Control Release. 2023 Nov;363:361-375. doi: 10.1016/j.jconrel.2023.09.042.

58. Han J, Park JH. Modulation of immune cells with mRNA nanoformulations for cancer immunotherapy. Curr Opin Biotechnol. 2023 Dec;84:103014. doi: 10.1016/j.copbio.2023.103014.

59. Feng W, Shi W, Cui Y, Xu J, Liu S, Gao H, Zhu S, Liu Y, Zhang H. Fe(III)-Shikonin supramolecular nanomedicines as immunogenic cell death stimulants and multifunctional immunoadjuvants for tumor vaccination. Theranostics. 2023 Sep 25;13(15):5266-5289. doi: 10.7150/thno.81650.

60. He JJ, Li QQ, Zhao C, Zhou J, Wu J, Zhang HB, Zhao YQ, Zhang HH, Lei TY, Zhao XY, You Z, Song QB, Xu B. Advancement and Applications of Nanotherapy for Cancer Immune Microenvironment. Curr Med Sci. 2023 Aug;43(4):631-646. doi: 10.1007/s11596-023-2763-0.

61. Chen YT, Luo YX, Chan SH, Chiu WY, Yang HW. Dual antibody-aided mesoporous nanoreactor for H<sub>2</sub>O<sub>2</sub> self-supplying chemodynamic therapy and checkpoint blockade immunotherapy in triple-negative breast cancer. J Nanobiotechnology. 2023 Oct 24;21(1):385. doi: 10.1186/s12951-023-02154-0.

62. Yang G, Pan X, Feng W, Yao Q, Jiang F, Du F, Zhou X, Xie J, Yuan X. Engineering Au<sub>44</sub> Nanoclusters for NIR-II Luminescence Imaging-Guided Photoactivatable Cancer Immunotherapy. ACS Nano. 2023 Aug 22;17(16):15605-15614.

63. doi: 10.1021/acsnano.3c02370.

64. S K P. Cancer reduction in mice with Prakasine nanomedicine immunotherapy. Artif Cells Nanomed Biotechnol. 2023 Dec;51(1):572-589. doi: 10.1080/21691401.2023.2270023.

65. Wang F, Pu K, Li J. Activating Nanomedicines with Electromagnetic Energy for Deep-Tissue Induction of Immunogenic Cell Death in Cancer Immunotherapy. Small Methods. 2023 May;7(5):e2201083. doi: 10.1002/smtd.202201083.

66. Synoradzki KJ, Paduszyńska N, Solnik M, Toro MD, Bilmin K, Bylina E, Rutkowski P, Yousef YA, Bucolo C, Zweifel SA, Reibaldi M, Fiedorowicz M, Czarnecka AM. From

Molecular Biology to Novel Immunotherapies and Nanomedicine in Uveal Melanoma. Curr Oncol. 2024 Feb 1;31(2):778-800. doi: 10.3390/curroncol31020058.

67. Zhang H, Chen K, Guo K, Tao J, Song L, Ren S, Zhao Y, Teng Z, Qiu W, Wang Z. Multimodal Imaging-Guided Photoimmunotherapy of Pancreatic Cancer by Organosilica Nanomedicine. Adv Healthc Mater. 2024 Jan;13(2):e2302195. doi: 10.1002/adhm.202302195.
68. Zhang L, Wang J, Cui H, Zheng H, Yin X, Lin J, Wang Y, Zhao Y, Li H, Chen Q. Simultaneous Knockdown of Immune Suppressive Markers by Tumor Microenvironment- Responsive Multifaceted Prodrug Nanomedicine. ACS Appl Mater Interfaces. 2023 Mar 15;15(10):12864-12881. doi: 10.1021/acsami.3c00986.
69. Hofstraat SR, Anbergen T, der Meel RV. Nanomedicine approaches for in vivo cancer immunotherapy. Nanomedicine (Lond). 2023 Oct;18(23):1607-1611. doi: 10.2217/nnm-2023-0230. Epub 2023 Sep 19.
70. Zhou H, Yu CY, Wei H. Liposome-based nanomedicine for immune checkpoint blocking therapy and combinatory cancer therapy. Int J Pharm. 2024 Mar 5;652:123818. doi: 10.1016/j.ijpharm.2024.123818.
71. Chang R, Li T, Fu Y, Chen Z, He Y, Sun X, Deng Y, Zhong Y, Xie Z, Yang Y, Liu J, Chen X, Liu H, Zhao Y. A PD-L1 targeting nanotheranostic for effective photoacoustic imaging guided photothermal-immunotherapy of tumor. J Mater Chem B. 2023 Sep 13;11(35):8492-8505. doi: 10.1039/d3tb00221g.
72. Kudruk S, Forsyth CM, Dion MZ, Hedlund Orbeck JK, Luo J, Klein RS, Kim AH, Heimberger AB, Mirkin CA, Stegh AH, Artzi N. Multimodal neuro-nanotechnology: Challenging the existing paradigm in glioblastoma therapy. Proc Natl Acad Sci U S A. 2024 Feb 20;121(8):e2306973121. doi: 10.1073/pnas.2306973121.
73. Feng X, Chen Z, Liu Z, Fu X, Song H, Zhang Q. Self-delivery photodynamic-hypoxia alleviating nanomedicine synergizes with anti-PD-L1 for câncer immunotherapy. Int J Pharm. 2023 May 25;639:122970. doi: 10.1016/j.ijpharm.2023.122970.
74. Zhang R, Xu H, Yao Y, Ran G, Zhang W, Zhang J, Sessler JL, Gao S, Zhang JL. Nickel(II) Phototheranostics: A Case Study in Photoactivated H Enhanced Immunotherapy. J Am Chem Soc. 2023 Oct25;145(42):23257-23274. doi: 10.1021/jacs.3c08181.
75. Li J, Han X, Gao S, Yan Y, Li X, Wang H. Tumor microenvironment-responsive DNA-based nanomedicine triggers innate sensing for enhanced immunotherapy. J Nanobiotechnology. 2023 Oct 19;21(1):382. doi: 10.1186/s12951-023-02132-6.
76. Li Y, Wu Y, Fang Z, Zhang Y, Ding H, Ren L, Zhang L, Gong Q, Gu Z, Luo K. Dendritic Nanomedicine with Boronate Bonds for Augmented Chemo-Immunotherapy via Synergistic Modulation of Tumor Immune Microenvironment. Adv Mater. 2024 Jan;36(2):e2307263. doi: 10.1002/adma.202307263.
77. Xing Y, Yang J, Wang Y, Wang C, Pan Z, Liu FL, Liu Y, Liu Q. Remodeling Tumor Immunogenicity with Dual-Activatable Binary CRISPR Nanomedicine for CancerImmunotherapy. ACS Nano. 2023 Mar 28;17(6):5713-5726. doi: 10.1021/acsnano.2c12107.

78. Ji S, Huang L, Chang S, Sun X, Liu H, Li A, Jin Y, Fei H. Albumin pre-opsonized membrane-active iPep nanomedicine potentiates chemo to immunotherapy of cancer. Biomaterials. 2023 Oct;301:122269. doi: 10.1016/j.biomaterials.2023.122269.

79. Li X, Duan Z, Li Z, Gu L, Li Y, Gong Q, Gu Z, Luo K. Dendritic polymer-functionalized nanomedicine potentiates immunotherapy via lethal energy crisis- induced PD-L1 degradation. Biomaterials. 2023 Nov;302:122294. doi: 10.1016/j.biomaterials.2023.122294.

80. Sun Z, Wen H, Zhang Z, Xu W, Bao M, Mo H, Hua X, Niu J, Song J, Kang M, Wang D, Tang BZ. Acceptor engineering-facilitated versatile AIEgen for mitochondria-targeted multimodal imaging-guided cancer photoimmunotherapy. Biomaterials. 2023 Oct;301:122276. doi: 10.1016/j.biomaterials.2023.122276.

81. Zu M, Ma Y, Zhang J, Sun J, Shahbazi MA, Pan G, Reis RL, Kundu SC, Liu J, Xiao B. An Oral Nanomedicine Elicits In Situ Vaccination Effect Against Colorectal Cancer. ACS Nano. 2024 Jan 30;18(4):3651-3668. doi: 10.1021/acsnano.3c11436.

82. Liu Y, Qi P, Chen G, Lang Z, Wang J, Wang X. Nanoreactor based on single- atom nanoenzymes promotes ferroptosis for cancer immunotherapy. Biomater Adv. 2024 Feb;157:213758. doi: 10.1016/j.bioadv.2024.213758.

83. Li T, Guo L, Li J, Mu X, Liu L, Song S, Luo N, Zhang Q, Zheng B, Jin G. Precision USPIO-PEG-SLe<sup>x</sup> Nanotheranostic Agent Targeted Photothermal Therapy for Enhanced Anti-PD-L1 Immunotherapy to Treat Immunotherapy Resistance. Int J Nanomedicine. 2024 Feb 7;19:1249-1272. doi: 10.2147/IJN.S445879.

84. Gao H, Qi X, Zhang J, Wang N, Xin J, Jiao D, Liu K, Qi J, Guan Y, Ding D. Smart One-for-All Agent with Adaptive Functions for Improving Photoacoustic /Fluorescence Imaging-Guided Photodynamic Immunotherapy. Small Methods. 2023 May;7(5):e2201582. doi: 10.1002/smtd.202201582.

85. Zhang P, Chen H, Chen C, Liu X, Cheng H, Wu Y, Wang X, Liu G, Zeng Y. Bioinspired immuno-radio-enhancers toward synergistic nanomedicine through radiation-induced abscopal effects and immunocheckpoint blockade therapies. Biomater Sci. 2023 Nov 7;11(22):7327-7338. doi: 10.1039/d3bm01144e.

86. Tiwari P, Shukla RP, Yadav K, Panwar D, Agarwal N, Kumar A, Singh N, Bakshi AK, Marwaha D, Gautam S, Rai N, Mishra PR. Exploring nanocarriers as innovative materials for advanced drug delivery strategies in onco-immunotherapies. J Mol Graph Model. 2024 May;128:108702. doi: 10.1016/j.jmgm.2024.108702.