International Journal of Nanomedicine

Dovepress
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REVIEW

Synergistic Potential of Nanomedicine in Prostate Cancer Immunotherapy: Breakthroughs and Prospects

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Abstract: Given the global prevalence of prostate cancer in men, it is crucial to explore more effective treatment strategies. Recently, immunotherapy has emerged as a promising cancer treatment due to its unique mechanism of action and potential long-term effectiveness. However, its limited efficacy in prostate cancer has prompted renewed interest in developing strategies to improve immunotherapy outcomes. Nanomedicine offers a novel perspective on cancer treatment with its unique size effects and surface properties. By employing targeted delivery, controlled release, and enhanced immunogenicity, nanoparticles can be synergized with nanomedicine platforms to amplify the effectiveness of immunotherapy in treating prostate cancer. Simultaneously, nanotechnology can address the limitations of immunotherapy and the challenges of immune escape and tumor microenvironment regulation. Additionally, the synergistic effects of combining nanomedicine with other therapies offer promising clinical outcomes. Innovative applications of nanomedicine include smart nanocarriers, stimulus-responsive systems, and precision medicine approaches to overcome translational obstacles in prostate cancer immunotherapy. This review highlights the transformative potential of nanomedicine in enhancing prostate cancer immunotherapy and emphasizes the need for interdisciplinary collaboration to drive research and clinical applications forward.

Keywords: prostate cancer, nanomedicine, immunotherapy, TME

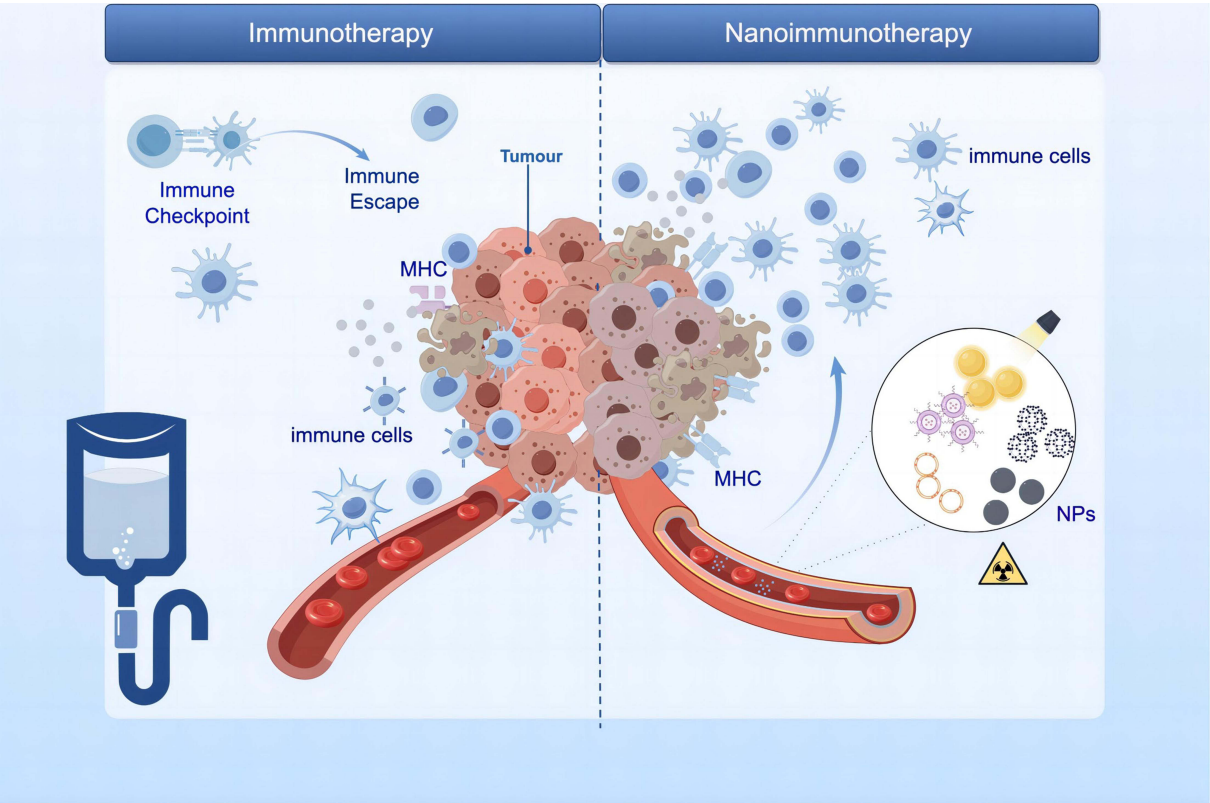
Introduction

Prostate cancer is the second most common malignancy in men worldwide and is a leading cause of death among males.[1] Androgen deprivation therapy (ADT) is the main treatment for advanced prostate cancer. However, most patients who receive ADT ultimately progress to castration-resistant prostate cancer (CRPC), with a median survival of less than two years.[2] Recent advancements in treatment have moderately improved survival rates for CRPC patients. However, the overall prognosis remains poor, and advanced prostate cancer is currently untreatable.[3,4] Hence, advanced treatment strategies are required to improve patient survival and prognosis.

The development of cancer immunotherapy has represented a significant milestone in oncology.[5,6] Immunotherapy, encompassing immune checkpoint inhibitors, antibody–drug conjugates (ADCs), cell therapy, and vaccine therapy, activate or regulate the immune system to eliminate cancer cells and achieve therapeutic effects.[7,8] The 2018 Nobel Prize in Physiology or Medicine was awarded for groundbreaking research on immune checkpoint molecules, specifically cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and programmed death receptor 1 (PD-1), which have significantly advanced the field of immunotherapy.[9] Although immunotherapy has become an important tool in prostate cancer treatment, activating the immune system to recognize and destroy cancer cells, it faces several challenges, including

Received: 28 February 2024
Accepted: 16 August 2024
Published: 2 October 2024

Graphical Abstract



immune escape mechanisms that allow cancer cells to evade surveillance and attack by the immune system, immune-related side effects caused by treatment,[10] and inconsistent efficacy among patients.[11] Therefore, an urgent need exists to develop new treatment strategies to improve immunotherapy outcomes.

Nanomedicine has shown great potential in this context as the application of nanotechnology in tumor therapy.[12] Indeed, nanotechnology holds immense promise in advancing the treatment,[13,14] prevention,[15,16] monitoring,[17] and management of biological diseases.[18,19] By integrating nano- and drug technologies, nanotechnology facilitates the development of drug delivery systems and enhances immunotherapy effectiveness by influencing the microbiome, enabling photothermal and photogenetic therapy, and facilitating gene therapy.[20,21] To specifically address the ineffectiveness of checkpoint blockade in "cold" tumors, nanomedicine can regulate the immune and mechanical properties of the tumor microenvironment (TME) to enhance radiotherapy/radiopharmacology.[22] Notably, combining immunotherapy with traditional therapies, such as chemotherapy or radiation therapy, can leverage the strengths and mitigate the weaknesses of each individual treatment. Moreover, by integrating immunotherapeutic modalities and nanomaterials with other treatment modalities, novel opportunities for enhanced cancer therapy may be realized. Therefore, this review discusses the role, synergistic approach, clinical transformation, and future directions of nanotechnology in prostate cancer immunotherapy.

Mechanisms of Nanomedical Applications in Immunotherapy of Prostate Cancer

Traditional ADT exhibits suboptimal efficacy in patients with CRPC, necessitating the development of more efficacious treatment modalities to augment prostate cancer management. Prostate cancer is characterized by its heterogeneity[23] and propensity for drug resistance,[24] resulting in slow clinical progression and complicating traditional chemotherapy efforts, prone to recurrence and regeneration.[25] The integration of nanomedicine into prostate cancer immunotherapy is

a promising approach for improving therapeutic efficacy while reducing adverse reactions. This section explores the synergistic potential of nanodrug platforms, such as nanoparticles, liposomes, and dendrimers, in prostate cancer immunotherapy. We discuss their mechanisms of action, including targeted delivery, controlled release, and enhanced immunogenicity, as well as recent advances and key studies demonstrating their effectiveness in the field.

Cancer Immunotherapy Mechanisms

Innate immunity is the body's first line of defense, comprising innate immune cells and soluble recognition molecules, such as natural antibodies and lectins. This process does not depend on antigen specificity and is not caused by brief induction.[26] When the body's initial barrier is breached, an adaptive immune response is triggered, involving the production of B cells that specifically target antigens and secrete antibodies and the activation of cytotoxic T cells. These cells secrete immune mediators and effector molecules, such as cytokines and chemokines, to eliminate antigens, pathogens, infected and cancer cells.[27] In the adaptive immune system, antigen-presenting cells (APCs) constantly eliminate exogenous or endogenous antigens, pathogens, infected and cancer cells. The exogenous antigens are primarily phagocytosed and processed by immature dendritic cells (DCs). During this process, the DCs mature and present target antigens to T cells via major histocompatibility complex (MHC) I or II molecules.[28]

Three key pathways for T cell activation include MHC I or II complexes binding T cell receptors, surface co-stimulatory molecule expression, and the secretion of cytokines, such as interleukin (IL)-12 and interferon (IFN)-γ. Different populations of T cells, such as helper T cells ($CD4^+$), cytotoxic T cells ($CD8^+$), memory T cells, and regulatory T cells, participate in the immune response. $CD4^+$ T helper cells can differentiate into various subtypes, such as Th1 cells (secrete IFN-γ and tumor necrosis factor (TNF)-α), Th2 cells (secrete IL-4, IL-5, and IL-13), and Th17 cells (secrete IL-17), which help activate cytotoxic $CD8^+$ cells and other innate immune cells to destroy tumor cells.[29]

Memory T cells form after antigen exposure and circulate through the body to provide long-term protection against foreign antigens. Moreover, antigen cross-presentation is an important aspect of the immune process, allowing extracellular antigens to be presented on MHC I molecules. This is a unique function of DCs that stimulates the immune system to eliminate target antigens such as tumor cells.[30]

Nanomedicine Platforms in Prostate Cancer Immunotherapy

Nanomedicine emerged as a cutting-edge platform for cancer treatment, offering targeted delivery of nanoparticles that induce superior antitumor responses while mitigating toxicity and associated costs. Various nanoparticles, such as liposomes,[31] polymer-based nanoparticles (NPs),[32] gold nanoparticles (AuNPs),[33] magnetic nanoparticles (MNPs),[34] silica particles (SNPs),[35] quantum dots (QDs),[36] carbon nanotubes (CNTs),[37] and mixed particles, are utilized for prostate cancer drug delivery (Figure 1 by Figdraw). These nanoparticles employ passive[38,39] or active targeting to enhance immunogenicity.[40] As important nanomaterials with high porosity, versatility, and biocompatibility, the ordered porous structure of nanomaterials (nMOFs) can avoid self-quenching of photosensitized agents and promote the diffusion of reactive oxygen species (ROS), improving the effect of photodynamic therapy and eliciting a cytotoxic effect. Its mediated low-dose radiation therapy can be combined with anti-programmed death ligand 1 (PDL1) antibodies to extend the local therapeutic effect of radiation therapy to distant tumors. Additionally, nMOFs can be combined with other forms of immunotherapy (eg, STING agonists or CpG oligonucleotides) to generate systemic anti-tumor immunity.[41] Liposomes,[42] polymerized nanoparticles, and other drug delivery vehicles effectively encapsulate lipophilic anticancer drugs, creating a protective barrier between the organism and the drug. Upon degradation, these vehicles release the drug contents,[43] exhibiting targeted delivery and safeguarding against drug degradation in experimental settings. This mechanism ensures drug accumulation within the tumor, enhancing efficacy.[44] The unique properties of nanocarriers in terms of size, surface charge, and ability to functionalize with targeted ligands make them ideal for overcoming the biological barriers that typically limit drug efficacy to solid tumors. The classification of nanocarrier systems is presented in Table 1.

Nanoparticle-mediated multimodal therapeutic strategies, such as chemodynamic therapy (CDT), sonodynamic therapy (SDT), photodynamic therapy (PDT), and radiation therapy (RT), provide a target for immune cell attack by inducing ROS production, directly impacting tumor cell survival and enhancing their immunogenicity. The application of

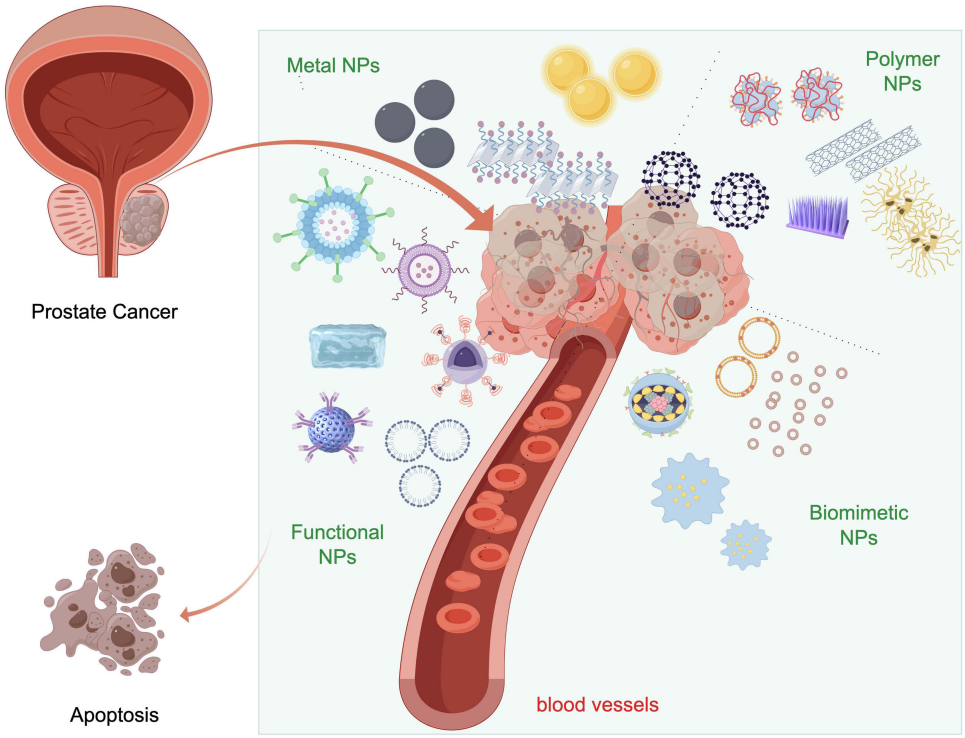


Figure 1 Optimization strategies of nanoparticles for the treatment of prostate cancer.

these therapeutic tools enhances the direct clearance of tumor cells while helping establish long-term immune memory, improving the durability and effectiveness of treatment (Figure 2 by Figdraw).

The potential of nanoparticles in modulating immune responses through multiple mechanisms in prostate cancer therapy is significant. This highlights the complex interactions of nanoparticles in regulating the TME and provides new insights regarding the mechanisms underlying tumor immune evasion to help guide the development of novel

Table 1 Classification of Nanodrug Delivery Systems and Their Application in the Treatment of Prostate Cancer

Types of nanosystems	Target mechanism	Research progress	Advantages	Boundedness	References
Liposomes	Passive targeting/ active targeting	In multiple clinical trials	Stronger antitumor activity and lower adverse reactions	High biocompatibility, easy to remove or biodegrade, flexible size and shape, high drug loading capacity, but with surface modification difficulty	[45]
PLGA	Passive targeting/ active targeting	Some animal tests have been carried out	Low toxicity, high biocompatibility		[46]
Dendrimers	Passive targeting	Still in the lab	High loading capacity and delivery capacity of therapeutic agent		[47]
Polymeric micelles	Active targeting	Partly entered clinical trails	Long drug cycle time, Self-assembly of polymers into nanoaggregates		[48]

(*Continued*)

Table 1 (Continued).

Types of nanosystems	Target mechanism	Research progress	Advantages	Boundedness	References
AuNPs	Active targeting	In preclinical study	Nontoxicity, overcoming drug resistance	Limited biocompatibility, difficult to clear from the body, accumulate in organs like the liver and spleen, difficult to control shape and size precisely, limited space for drug binding, but with a more flexible functional surface	[49–51]
MNPs	Active targeting	In preclinical study	High biocompatibility, participation in magnetic hyperthermia may induce tumor thermal ablation		[52]
SNPs	Passive targeting/ active targeting	In multiple clinical trials	High stability, modifiable particle and aperture, large surface area, large porosity		[53,54]
QDs	Passive targeting/ Active targeting	Some animal tests have been carried out	High water solubility, High biocompatibility		[55]
CNTs	Active targeting	Some animal tests have been carried out	High drug loading capacity		[56]

immunotherapies. This multimodal therapeutic approach may be important for overcoming the immunosuppressive microenvironment of prostate cancer and activating a potent antitumor immune response, improving efficacy. In addition, the modulation of the cytokine milieu and its effect on macrophage polarization reveals the possibility of enhancing tumor clearance by precisely modulating the immune response.

Macrophages, key immunoregulatory cells in the TME, differentiate into pro-inflammatory M1-type or anti-inflammatory M2-type depending on the signals received. Nanoparticle-based therapeutics play an important role in the antitumor immune response by modulating cytokine expression patterns within the TME, including upregulating IL-12 and TNF-α levels while reducing IL-10 and TNF-δ expression, influencing macrophage polarization. For example, cyclic RGD peptide-functionalized and manganese-doped eumelanin-like nanocomposites (RMnMels) can be used for high-temperature immunotherapy in PC3 prostate cancer to enhance anti-tumor immune responses by promoting the repolarization of M2 to M1 macrophages by clearing ROS and reshaping the immunosuppressive TME.[57]

Further investigation into the dynamic in vivo distribution of nanoparticles, their long-term immune effects, and potential systemic immunomodulatory impacts will facilitate the design of safer, more effective nanomedicines, paving the way for innovative approaches to prostate cancer treatment.

Nanomedical Enhancement in Cancer Immunotherapy

Targeted Delivery: Nanodrug platforms can identify and bind specific biomarkers overexpressed in prostate cancer cells, such as prostate-specific membrane antigen (PSMA), ensuring that the therapeutic agent is delivered directly to the tumor site. This can improve treatment specificity and efficacy.[58,59]

Controlled Release: During targeted delivery of the nanomedicine platform to the tumor site, nanocarriers can encapsulate the immunotherapeutic agent, facilitating its protected transport in the bloodstream and release in a controlled manner at the tumor site. This controlled release mechanism can be designed to respond to specific stimuli within the TME, such as pH changes or enzyme activity, ensuring the spatially and temporally controlled release of therapeutic agents.[60]

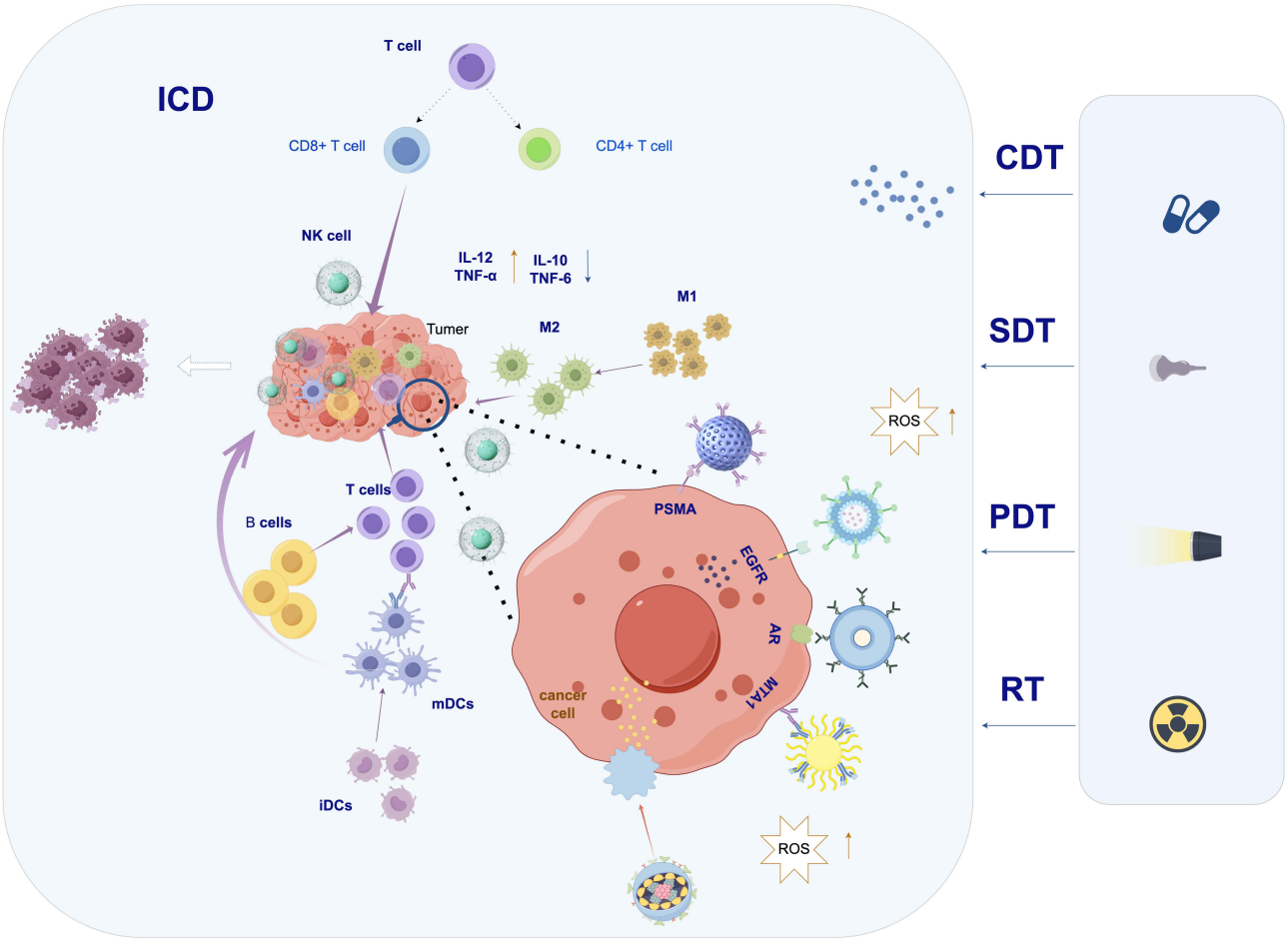


Figure 2 Nanomedicines can be utilized to boost tumor immunogenicity in combination with CDT, SDT, PDT, and RT.

Enhanced Immunogenicity: Certain nanocarriers are designed to deliver drugs that induce immunogenic cell death (ICD) by promoting the release of tumor antigens and stimulating the immune system to recognize and attack danger signals, enhancing tumor cell immunogenicity.[61]

Recent Advancements

Recent studies have highlighted the effectiveness of nanomedicines in improving the efficacy of immunotherapy for prostate cancer. For example, clinical pilot studies have demonstrated the promise of gold-nanoshell-localized photothermal ablation for focal treatment of prostate tumors, highlighting the ability of nanomedicine to deliver highly targeted and effective treatment options with minimal side effects.[62] In addition, the development of PSMA-targeted nanomedicines for treating advanced prostate cancer shows great potential for bridging the gap between nanomedicine research and clinical practice, providing new strategies for disease management.[58]

Another innovative approach involves using extracellular vesicles from *Akkermansia muciniphila*, which induce antitumor immunity against prostate cancer by modulating $CD8^+$ T cells and macrophages, demonstrating the potential of nanomedicine to harness microbiota in cancer treatment.[20] Additionally, urokinase plasminogen activator receptor (uPAR)-targeted nanocarriers based on exosomes have been explored. Specifically, the Exo-PMA/Fe-HSA@DOX system is loaded with doxorubicin and achieves synergistic therapy via chemodynamic treatment and low-dose chemotherapy in prostate cancer (PCa). This nanosystem can significantly enhance internalization in vitro and block the epidermal growth factor receptor (EGFR)/protein kinase B (AKT)/nuclear factor (NF)-κB signaling pathways.[63]

The integration of nanomedicine into prostate cancer immunotherapy is at the forefront of current research with the potential to significantly improve patient outcomes. Nanomedical platforms offer promising and feasible solutions to overcome the limitations of current therapeutic modalities by enhancing the targeted delivery, controlled release, and immunogenicity of therapeutic drugs. Ongoing research and clinical trials are essential to determine the full potential of these innovative therapies for treating prostate cancer.

Applying Nanotechnology to Overcome Immunotherapy Limitations

The immunological processes involved in cancer vaccine platforms, PD-1/PD-L1 inhibitors, and CAR-T cells are presented in Figure 3 (By Figdraw). Clinical studies related to immunotherapy are listed in Table 2. Although immunotherapy has achieved some positive results, its efficacy is often hampered by the immunosuppressive nature of the TME and immune escape. Recent advances in nanomedicine have provided innovative strategies to overcome these

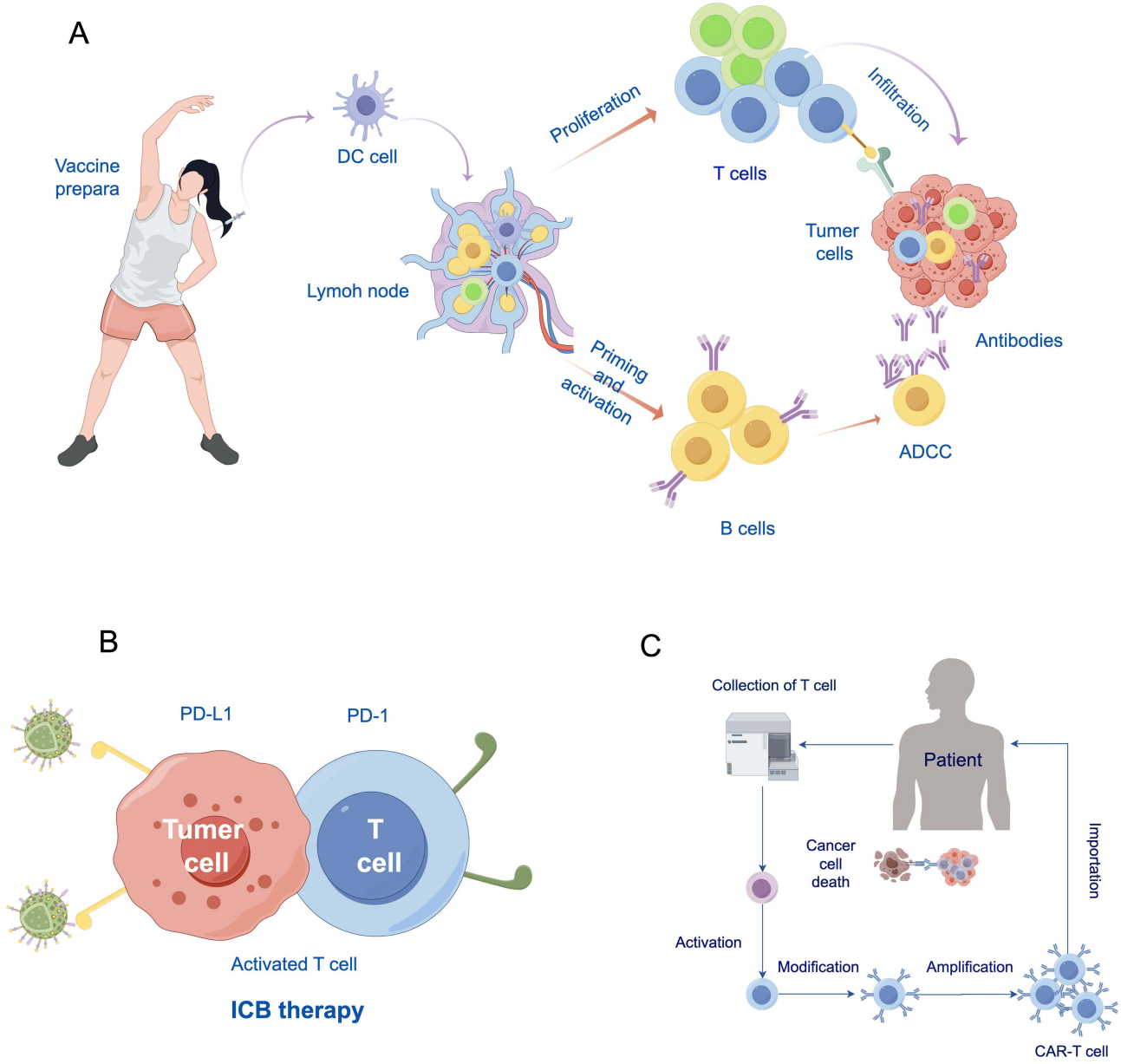


Figure 3 (**A**). Cancer vaccine platforms and interactions in the immune system; (**B**). PD-1/PD-L1 are involved in immune checkpoint blockade (ICB) therapy; (**C**).CAR-T cell immunotherapy process.

Table 2 Immunotherapy Trials for Prostate Cancer

Drugs/cells	Target/mechanism	Treatment type	Trial phase	Trial identifier
Nivolumab	Prevents PD-L1 and PD-L2 from inhibiting the action of T cells by binding to PD-1.	Anti-PD1 antibody	II	NCT03651271
Pembrolizumab	Prevents PD-L1 and PD-L2 from inhibiting the action of T cells by binding to PD-1.	Anti-PD1 antibody	II	NCT04104893
Ipilimumab	A humanized monoclonal antibody that inhibits cytotoxic T lymphocyte antigen-4 (CTLA-4).	Anti-CTLA-4 antibody	III	NCT01057810
Nivolumab, ipilimumab	To evaluate the efficacy of PD-1 inhibitor in combination with CTLA4 inhibitor.	Dual PD-1 * CTLA-4 inhibitors	II	NCT03061539
PSCA-CAR T cells	Autologous T lymphocytes expressing anti-PSCA-CAR -4-1BB/TCRzCD19t, in conjunction with a regimen of chemotherapy drugs including cyclophosphamide, fludarabine, and fludarabine phosphate.	Chimeric antigen receptor T cells	I	NCT03873805
PD1-PSMA-CAR T cells	The study explores the efficacy of non-viral programmed cell death protein-1 (PD-1) integrated anti-prostate-specific-membrane-antigen (PSMA) CAR T cell immunotherapy.	Chimeric antigen receptor T cells	I	NCT05354375
PSMA-targeted CAR T cells	CAR T cell immunotherapy with chimeric antigen receptor targeting PSMA.	Chimeric antigen receptor T cells	I	NCT05354375
TABP EIC	New therapy combining anti-PSMA-targeted CAR NK cell immunotherapy with cyclophosphamide and fludarabine chemotherapy.	Chimeric antigen receptor natural killer (NK) cells	I	NCT03692663
UV1	Using a combination of human telomerase fragment, UV1 peptide, and GM-CSF to target cancer cells immunologically.	Synthetic peptide vaccine	I/II	NCT01784913
NY-ESO-1 protein	NY-ESO-1 protein is paired with CpG 7909 adjuvant to boost immune response.	Peptide vaccine	I	NCT00292045
pTVG-HP vaccine with or without pTVG-AR DNA vaccine and pembrolizumab	Using pembrolizumab to target PAP and block PD-1 concurrently to enhance tumor-specific CD8+ T cells.	PAP-targeted DNA vaccine	II	NCT04090528
ETBX-071, ETBX-061, and ETBX-051	A mix of vaccines that trigger T cell immune responses against tumor-associated antigens.	Mixture of adenovirus vaccines	I	NCT03481816

barriers and enhance the therapeutic potential of prostate cancer immunotherapy. Advanced nanotechnology enables precise targeting of TME components tailored to nanoparticle requirements. This ability to differentiate between healthy and malignant tissues facilitates TME modulation to impede tumor progression. Moreover, these nanoparticles boast prolonged retention, high bioavailability, and low toxicity, further enhancing their therapeutic potential.

Role of Nanomedicine in TME Modulation

Nanomedicine plays a key role in modulating the TME to improve the immune response in prostate cancer. By targeting the unique properties of the TME, such as its acidic pH, hypoxic conditions, and high interstitial pressure, nanomaterials can enhance the penetration and retention of immunotherapeutics. This approach improves therapeutic efficacy and reduces systemic adverse reactions.

The immunosuppressive TME and immune escape mechanisms significantly limit the effectiveness of immunotherapy for prostate cancer. Nanomedical approaches have been developed to specifically target and modulate the TME, enhancing the immune response of tumor cells. For example, the two-pronged strategy using pH-driven membrane anchoring nanophotosensitizers has shown promise in stimulating ICD and isolating immune checkpoints, converting "cold" tumors into "hot" tumors, ultimately enhancing the efficacy of photoimmunotherapy for prostate cancer.[64]

Supramolecular nanotechnology materials have been developed to modify the immunosuppressive TME, working in tandem with immune checkpoint-blocking therapy to achieve enhanced cancer immunotherapy outcomes.[65] After vaccination, DCs play a vital role in capturing, processing, and presenting tumor antigens, ultimately activating T cells that suppress tumor cells. Moreover, activated B cells contribute to tumor cell death through antibody-dependent cell-mediated cytotoxicity. Engineered metal-phenol networks have emerged as a novel strategy to regulate the TME, aiming to enhance cancer treatment by reversing its immunosuppressive nature and rendering tumors sensitive to immunotherapy.

Enhancing Delivery and Efficacy of Immunotherapeutic Agents

The delivery and efficacy of immune checkpoint inhibitors, cancer vaccines, and T-cell therapies are important components of immunotherapy. Nanoparticles can improve the efficacy of these drugs by delivering them directly to the tumor site, minimizing systemic toxicity and increasing their therapeutic efficacy. In mouse prostate tumors that develop in the context of prostate-specific PTEN and p53 deletion, the activation of bovine serum albumin (BSA)-nanoparticles by cabozantinib initiates their uptake by tumor-infiltrating neutrophils (TINs) rather than peripheral neutrophils, avoiding RES uptake in the liver and enabling more efficient intraterritormal payload delivery. Given that this platform minimizes off-target toxicity, it can also be used to test new combination therapies.[66]

PSMA-targeted nanoparticles have shown great potential in treating prostate cancer. PSMA is highly expressed in prostate cancer cells, providing a precise target for nanoparticles to maximize therapeutic efficacy and minimize side effects in healthy tissue. Meanwhile, a co-delivery system based on stem cell membrane-coated polydopamine nanoparticles significantly improves the targeting and efficacy of doxorubicin and PD-L1 siRNA.[67] PSMA-targeted melanin-like nanoparticles combine photothermal therapy and drug delivery functions, achieving up to a 90% apoptosis rate in prostate cancer cells in vitro.[68] Glutamate-urea-based PSMA-targeted poly(lactic-co-glycolic) acid (PLGA) nanoparticles deliver docetaxel, effectively doubling the anticancer efficacy of the drug.[69] Additionally, PSMA-targeted nanoparticles functionalized with a urea-based inhibitor demonstrate good biocompatibility and high targeting efficiency, reducing tumor viability.[70]

In radioparticle therapy, PSMA-targeted alpha therapy (TAT) using 225Ac-PSMA-I&T has shown promising anti-tumor effects in patients with advanced metastatic CRPC (mCRPC). In one study, 11/14 patients experienced a significant decrease in PSA levels, with a $\geq$ 50% reduction in seven patients, supporting the therapeutic efficacy.[71] Hence, PSMA-targeted nanoparticles hold great promise for prostate cancer diagnosis and treatment. However, many technical and clinical challenges must be overcome to maximize their clinical application.[72]

In addition, approaches such as mRNA- and hydrogel-based CAR-T-cell delivery, photothermal remodeling, and TME-based CAR-T-cell therapy have shown promise in enhancing the efficacy of CAR-T therapy. The integration of nanotechnology into immunotherapy holds the potential to overcome certain limitations of traditional immunotherapy, leading to improved therapeutic outcomes.[73]

Clinical Implications and Future Prospects

The combination of nanomedicine and immunotherapy for prostate cancer has great potential to improve patient prognosis. Clinical trials and preclinical studies have shown the promise of nanotechnology-based strategies in overcoming the limitations of current immunotherapy approaches. Future research should focus on the development of multifunctional nanosystems that can simultaneously target multiple aspects of the TME and the immune system, providing a comprehensive and novel strategy for combating prostate cancer with excellent clinical performance.

Synergistic Approach and Combination Therapy

In recent decades, single-mode treatment strategies, including chemotherapy, photodynamic therapy, and radiation therapy, have made significant medical advances in tumor suppression and patient survival.[74] However, these treatments have encountered many limitations in clinical application. Specifically, the rapid metabolic clearance and non-specific distribution of chemotherapeutic drugs significantly reduce their therapeutic efficiency and may trigger systemic toxicity reactions. Moreover, prolonged or repeated use of a drug can result in tumor cells developing therapeutic resistance.[75] Meanwhile, the effectiveness of photodynamic therapy in treating tumors is limited by the potential for irreversible light damage to normal tissues, the inherent heat tolerance of tumors, and the risk of tumor metastasis and recurrence. Moreover, hypoxic tumor cells are less sensitive to ionizing radiation. Monoimmunotherapy also faces off-target toxicity, inadequate immune responses, poorly sustained efficacy, and low immunogenicity, resulting in inadequate treatment outcomes.

However, combining immunotherapy with other treatment modalities, including chemotherapy, photodynamic therapy, radiation therapy, sonodynamic therapy, metabolic therapy, and microwave thermotherapy, has facilitated the development of synergistic treatment strategies. These modalities can achieve a super-additive treatment effect beyond single therapy or simple combination therapy, improving the overall efficacy of cancer treatment.

Recent advances have demonstrated the potential of nanomedicine to work synergistically with existing therapies such as chemotherapy, radiotherapy, and hormone therapy. Thus, combining nanomedicine and immunotherapy to treat prostate cancer is a promising frontier for improving treatment efficacy and overcoming the limitations of conventional treatments.

Combining Nanomedicine with Other Therapies

The rationale for combining nanomedicine with other therapies to treat prostate cancer lies in the multifaceted nature of the disease and its complex TME. Nanomedicine brings about targeted delivery mechanisms, improved bioavailability, and reduced systemic toxicity, which complement the mechanisms of action of traditional therapies. For example, polymerized nanomaterials designed for tumor-targeted combination therapy have demonstrated synergistic genotoxicity in prostate cancer through the combined delivery of chemotherapeutic agents, such as doxorubicin and 5-fluorouracil, enhancing cell cycle arrest, caspase-3 activation, and DNA damage.[76]

Chemotherapy

Conventional chemotherapy remains a cornerstone in prostate cancer treatment, relying on toxic drugs to eliminate cancer cells.[77] Widely used in clinical practice, traditional chemotherapeutic drugs suffer from a short plasma half-life and rapid distribution in healthy tissues and organs, leading to significant side effects. In addition, the limited retention and accumulation of drugs within tumors, coupled with the multidrug resistance (MDR) phenomena induced by chemotherapy, contribute to cancer cells developing resistance against structurally similar drug molecules, increasing the likelihood of treatment failure.[78] Therefore, more effective methods must be explored and developed to obtain greater clinical benefits. With the development of nanomedicine, the combination of multifunctional nanocarriers and radiotherapy has shown promising prospects. Strategies to improve the efficacy of nanomaterial-based chemotherapy include chemotherapy targeting specific suborganelles, chemotherapeutic drug enhancement at tumor sites, reversal of drug resistance mechanisms, and combination chemotherapy. Nanocarriers encapsulate chemotherapeutic drugs, shielding them from efflux pumps to increase intracellular drug concentrations.[79] By targeting tumor cells or blood vessels, these nanocarriers outperform traditional chemotherapy drugs with lower toxicity, mitigating multidrug resistance and enhancing drug efficacy while reducing side effects. Substances like borletoxins, doxorubicin, and actinomycin are utilized in preparing nanomedical drugs.[80] Moreover, some nanocarrier chemotherapeutic drugs, such as paclitaxel- and doxorubicin-containing liposomes, have been applied clinically with relatively mild adverse reactions and high safety.

Radiotherapy

Radiotherapy is a main treatment modality for prostate cancer that is used as a first-line treatment or in combination with surgery and chemotherapy.[81] Although effective, it has certain side effects as it cannot distinguish between normal and diseased tissues. Accordingly, many studies have focused on determining the effective dose to kill tumor cells without

causing additional damage to healthy tissues. Nanomedicine can also be applied to new drug delivery methods in CRT, and the low toxicity of nanomedicine carriers to normal tissues has been demonstrated experimentally.[82] Numerous studies have explored the benefits of nanomedicine delivery in improving chemoradiotherapy (CRT) and enhancing delivery to induce DNA damage directly near tumors to minimize drug off-target effects and the required radiation doses. Nanomaterials labeled with magnetic resonance imaging (MRI), positron emission tomography (PET), and computed tomography (CT) contrast agents can enhance imaging capabilities. Moreover, nanotechnology enables the preparation of nanoparticles to alleviate tumor hypoxia, regulate the immunosuppressive TME, and significantly enhance radiotherapy efficacy.[83,84]

Combination Therapy

Nanomedicine also plays an important role in combination therapy, with growing evidence supporting its ability to enhance the synergy between immunotherapy and radiotherapy. While most patients undergoing radiotherapy receive chemotherapy concurrently, ie, CRT, this combined approach often fails to eradicate the primary tumor, necessitating improved radiotherapy-based strategies. Emerging immunotherapies can clear tumors by activating the patient's immune system. In particular, CTLA-4, PD-1, and other immune checkpoints have been shown to improve clinical symptoms[85] while combinatorial radiotherapy and immunotherapy further enhance efficacy.[86] In preclinical models of metastatic prostate cancer, combining irradiation of metastatic cancer cells and anti-CTLA-4 antibody treatment effectively induced T-cell responses, enhancing local antitumor effects and responses to distant metastases. Thus, this combinatorial therapy has significant systemic immunological effects.[87] In the CRPC mouse model, the survival rate was improved by combined radiotherapy and anti-PD-1 or anti-PD-L1 treatment compared with monotherapy.[88] Radiotherapy can enhance immunotherapy in clinical practice,[89] as evidenced by MHC I up-regulation,[90] increased antigen availability,[91] and heightened cytokine release. Meanwhile, immune checkpoint inhibitors can enhance CRT.[92] Mechanisms underlying this synergy include sensitization of the TME prior to radiotherapy[93] or elicitation of an immune response sensitized to radiation.[94] Nanoparticles are crucial in this context as they facilitate targeted drug delivery and enhance antigen presentation by APCs.[95] In addition to enhancing the immunotherapeutic effect to improve treatments,[96] nanoparticles can also transport photosensitizers as complex delivery carriers of antibodies or radioisotopes for direct radiation delivery,[96] which can be activated by photothermal or photodynamic therapy.

The Au/Mn nanoparticle-Luteinizing Hormone-Releasing Hormone (AMNDs-LHRH) nanosystem is a sophisticated targeted therapeutic platform designed for multimodal imaging-guided photothermal therapy of prostate cancer. It boasts excellent targeting capabilities and efficient photothermal conversion, significantly enhancing the therapeutic effects of photothermal treatment for metastatic prostate cancer. Specifically, this system targets gonadotropin-releasing hormone receptor (GnRH-R)-positive prostate cancer cells and their metastases, facilitating accurate preoperative diagnosis via CT/MR imaging. Additionally, the system features fluorescence visualization for surgical navigation, minimal invasiveness, lack of drug resistance or side effects, and the potential to improve patients' quality of life. Consequently, the Au/Mn nanoparticle-LHRH nanosystem holds significant potential for clinical diagnosis and treatment of metastatic prostate cancer.[97] Alternatively, up-conversion can mark and stimulate DCs.[98] In addition, nanotechnology may synergistically enhance these two therapies by improving the responses of NK and B cells. In conclusion, nanotechnology exhibits promising synergy in combining immunotherapy and radiotherapy.

Multifunctional nanosystems not only improve drug bioavailability, enhance tumor-targeting capabilities, and reduce drug side effects but also offer a potential platform for treating and diagnosing metastatic prostate cancer. While prostate cancer and its metastases are typically detected using MRI, challenges arise due to discrepancies in detection methods, such as PET-CT and ECT.[99] Conventional contrast media are limited to single-mode imaging, whereas multifunctional nanosystems improve the accuracy of multimode imaging detection of metastatic prostate cancer, effectively guiding cancer treatment. Furthermore, multifunctional nanosystems demonstrate potent photothermal treatment effects, inducing tumor cell apoptosis by elevating the temperature of tumor cells through near-infrared light absorption and heat conversion, facilitating thermal ablation of tumor cells[100] with minimal invasiveness, no drug resistance, few side effects, and low toxicity.[101] Hence, multifunctional nanosystems present new possibilities for the diagnosis and treatment of prostate cancer, offering powerful targeting capabilities.

Case Studies and Clinical Trials Highlighting Synergistic Effects

Several case studies and clinical trials have demonstrated the synergistic potential of nanomedicines in combination with other cancer treatments. For example, nanodrug-driven PDT has been shown to trigger ICD and regulate the TME, improving the efficacy of cancer immunotherapy.[102] In addition, ongoing studies on vaccine therapy, CTLA-4 inhibitors, PD-1/PD-L1 inhibitors, and PSMA-targeted therapies have reported promising results as prostate cancer immunotherapy modalities and the indispensable role of nanomedicine in facilitating these approaches.[8] Recent studies have reported the utilization of combined immunotherapy and nanomedicine in clinical trials for cancer treatment (Table 3).

Future Prospects for Designing Multifunctional Nanosystems for Immunotherapy

Looking to the future, the design of multifunctional nanosystems has the potential to advance the development of prostate cancer immunotherapy. The development of vaccine-based immunotherapy regimens, such as PF-06753512, which targets prostate-specific antigens and uses immune checkpoint inhibitors, exemplifies the innovative approaches being explored. PF-06753512 is a vaccine-based immunotherapy regimen (VBIR) under development for treating patients with prostate cancer across various clinical stages. This regimen combines a vaccine approach with immune checkpoint inhibitors, utilizing novel administration methods, including electroporation of plasmid DNA (pDNA) encoding antigens and subcutaneous (SC) delivery of immune checkpoint inhibitors. In a Phase I open-label study, this strategy exhibited safety signals comparable to other immune checkpoint inhibitor combination trials in mCRPC, stimulating antigen-specific immunity across all cohorts and demonstrating modest antitumor activity in patients with biochemical recurrence (BCR) without the use of androgen deprivation therapy (ADT).[121] These strategies are designed to enhance antigen specificity, modulate immune responses, and achieve more effective and long-lasting antitumor effects.[121]

The synergy and fusion of nanomedicine and other therapeutic methods provide a promising avenue for improving the efficacy of immunotherapy for prostate cancer. By harnessing nanomedicine's unique properties, researchers and clinicians can more effectively target the TME, overcome drug resistance, and minimize adverse reactions. Continued exploration and clinical validation of these combination therapies will ensure that they reach their full potential in prostate cancer treatment.

Clinical Transformation and Challenges

Overview of Nanomedicine Products in Clinical Use or Trials

Products such as PSMA-targeted nanomedicines, nanoparticle-based siRNA, and chemotherapeutic drug delivery systems have shown potential in preclinical and early-stage clinical trials. These nanomedicines aim to improve targeted drug delivery through innovative strategies, such as photothermal therapy and targeted delivery of immunomodulators, to reduce adverse reactions and improve therapeutic efficacy.[122–125]

Nanoparticles have shown considerable promise in the diagnosis and treatment of prostate cancer. In diagnosis, nanoparticles can be used for biomarker detection, encompassing quantitative fluorescence nanosensors,[126] superparamagnetic iron oxide nanoparticles modified by chitosan, and sarcosine oxidase gold nanoparticles.[127] Additionally, nanoparticles have been applied in nuclear medicine, including in the assembly of aptamers from fluorophores[128] and utilizing Raman optical inspection platforms based on nanocolumns.[129] They may also contribute to imaging through gene amplification of nanoparticle tumor homing strategies.[130]

Nanomedicine products have also undergone a series of clinical transformations. In chemotherapy, nanoparticles can be used to deliver docetaxel,[131,132] cabatasel,[133] carbataxel combined with hyaluronic acid,[134] and other drugs. In radiotherapy, nanoparticles can facilitate X-ray source radiation by significantly increasing the radiosensitivity of cancer cells[135] or inhibiting the cloning potential of hypoxic prostate cancer cells.[136] They also have applications in image-guided surgery, PSMA receptor-targeting quantum dots,[137] and double infrared-near-infrared spectroscopy fluorescent and radio-guided probes.[138] In genetic and epigenetic therapies, nanotechnology facilitates the delivery of gold nanoparticles,[139] micelles,[140] and microRNA-197 inhibitors.[141] In pH-based strategies, nanotechnology can be used to coat calcium dioxide with polyacrylic acid[142] and cathepsin,[143] among other agents. Nanomedicines can also be used with natural compounds, such as doxorubicin, tanshinone,[144] and goniothalamin.[145] Additionally, nanotechnology can be

Table 3 Immunotherapy Combined with Nanomedicine in Cancer

Nanomaterial Type	Target Molecule	Mechanism of Action	Immune Response Type	Therapeutic Effect	Clinical Trial Phase	Safety and Toxicity	Advantages	Limitations	References
Gold Nanoparticles	Tumor-associated antigens	Delivery of immunostimulants	Cytotoxic T-cell response	Tumor shrinkage	Early clinical research	Low toxicity	High drug delivery efficiency	High production cost	[103]
Liposomes	Immune regulatory molecules	Blocking immune suppression pathways	ADCC	Increased survival rate	Phase I/II	Minimal adverse reactions	Reduced toxicity to normal tissues	Stability issues in vivo	[104]
Polymer Nanoparticles	Checkpoint inhibitors	Activation of T cells	Both cytotoxic and helper T-cell responses	Improvement in survival rates	Phase III	Potential immune reactions	Enhanced targeting specificity	Possible immune response	[105]
Metal-based DDS	PD-1/PD-L1 axis	Direct targeting of immune checkpoints	Enhanced antitumor immunity	Increased efficacy of checkpoint inhibitors	Preclinical trials	Varies with material	Precise targeting capability	Potential toxicity and clearance issues	[106]
Liposomal Systems	Clonal neoantigens	Elicit T-cell immunoreactivity	Sensitivity to immune checkpoint blockade	Durable clinical benefit	Preclinical	Generally safe with controlled release	Reduced systemic toxicity	Limited loading capacity for some drugs	[107]
Metal-based DDS	PD-1/PD-L1 axis	Direct targeting of immune checkpoints	Enhanced antitumor immunity	Increased efficacy of checkpoint inhibitors	Early-phase trials	Varies with material	Precise targeting capability	Potential toxicity and clearance issues	[108]
Liposomal Systems	Clonal neoantigens	Elicit T-cell immunoreactivity	Sensitivity to immune checkpoint blockade	Durable clinical benefit	Preclinical trials	Generally safe with controlled release	Reduced systemic toxicity	Limited loading capacity for some drugs	[107]
Polymer-based Nanocarriers	Tumor microenvironment modifiers	Alteration of tumor microenvironment	Modulation of immune cell infiltration	Improved therapeutic targeting	Preclinical trials	Low to moderate, depending on composition	Enhanced penetration and retention	Potential immunogenicity	[10]

(*Continued*)

https://doi.org/10.2147/IJN.S466396

Table 3 (Continued).

Nanomaterial Type	Target Molecule	Mechanism of Action	Immune Response Type	Therapeutic Effect	Clinical Trial Phase	Safety and Toxicity	Advantages	Limitations	References
Extracellular Vesicle Mimetics	Immune co-stimulatory signals	Enhancement of immune activation	Promotion of T and B cell responses	Augmentation of immunotherapy effects	Early research	Generally biocompatible	High specificity and reduced off-target effects	Production scalability	[109]
Hybrid Nanosystems	Multiple immune targets	Synergistic activation of immune pathways	Broad spectrum immune activation	Comprehensive immune response against tumors	Preclinical trials	–	Multiplexed therapeutic delivery	Complexity in design and manufacturing	[110]
Saponin Nanoparticles	Toll-Like Receptor Agonists	Improvement of vaccine immunomodulation	Enhanced neutralization and durability of immune response	Potentiation of vaccine efficacy	Preclinical trials	–	Broad application potential	Specific Th-responses dependent on formulation	[111]
Hyaluronic Acid Functionalized Hydrogel	Immunomodulatory microenvironment	Promotion of bone reconstruction via anti-inflammatory microenvironment	Anti-inflammatory response	Aids bone defect reconstruction	Preclinical trials	Biocompatible with minimal adverse effects	Innovative approach for bone repair	Limited to bone-related applications	[112]
Gold Nanoparticles in Radiation Therapy	MDA MB 231 Breast Cancer Model	Immunomodulation via radiation therapy enhancement	Induction of immune response to cancer cells	Potential improvement in radiation therapy efficacy	Experimental trials	–	Enhances the effect of radiation therapy	Specific to model studied; extrapolation needed	[113]
Nanoparticle Biomolecular Corona	Personalized immunomodulation	Impact on therapeutic outcomes through immune recognition	Person-specific immune recognition	Tailored therapeutic outcomes	Experimental trials	–	Personalized therapy potential	Complexity in predicting outcomes	[114]
Peptide-Based Nanovaccines	Prostate Cancer Antigens	Targeted delivery of antigens to immune cells	Augmented CD8+ T cell responses	Tumor growth inhibition	Preclinical trials	Safety profiles to be determined	High specificity and reduced off-target effects	Scalability and production challenges	[115]
PSMA-targeted Nanomedicine	Prostate Specific Membrane Antigen (PSMA)	Targeted drug delivery and combination therapy	–	Enhanced treatment efficacy and reduced adverse effects	–	–	Precise targeting of PCa cells	Biological barriers to effectiveness	[58]

Nanomedicine for Urologic Cancer	–	Combination of nanotechnology with immunotherapy	Enhanced efficacy and reduced toxicities	Precision medicine in urologic cancers	–	–	Enhanced treatment outcomes	Dose-limiting toxicities and low response rates	[59]
Akkermansia muciniphila-derived EVs	–	Modulation of CD8+ T cells and macrophages	Antitumor immunity	Reduced tumor burden without inducing toxicity	–	Well-tolerated	Efficient and biocompatible immunotherapeutic agent	Further validation required	[61]
Dendritic Cell Loaded Nanoparticles	MAGE-A2 long peptide	Target for tumor-specific T-cell-mediated immunotherapy	Enhanced T-cell immunity	Potential for personalized immunotherapy	–	–	Targeted immune activation	Limited clinical data available	[116]
PLGA Nanoparticles Co-Loaded with ICG and R848	–	Combination of photothermal therapy and immunotherapy	Enhanced antitumor immune response	Anti-tumor efficacy by combining therapies	–	–	Dual-functional approach	Further studies needed for clinical application	[117]
Immune Modulation via Senescence	–	Leveraging therapy-induced senescence for immunotherapy	Activation of immune surveillance	Sensitization to anti-PD-1 therapy	Research phase	Well-tolerated	Novel approach to convert "cold" tumors "hot"	Mechanism of action requires further elucidation	[118]
Extracellular Vesicles from Akkermansia muciniphila	–	Modulation of CD8+ T cells and macrophages	Antitumor immunity	Reduced tumor burden without inducing toxicity	–	Biocompatible	Efficient and biocompatible immunotherapeutic agent	–	[61]
TAM-Targeted Reeducation	–	Modulation of tumor-associated macrophages	Enhanced cancer immunotherapy	–	Research phase	–	Promising strategy for immunomodulation	–	[119]
STEAP1 CAR T Cell & IL-12 Therapy	STEAP1	Targeted CAR T cell therapy combined with IL-12	Enhanced antitumor immunity	Promising therapeutic outcomes in advanced PCa	Experimental phase	–	Innovative combination therapy	–	[120]

https://doi.org/10.2147/IJN.S466396

applied for bionic phosphatidylserine,[146] lentinan,[147] graphene oxide–peptide complexes,[148] and various nanomaterials to treat prostate cancer, including overcoming drug resistance of CRPC cells,[149] inhibiting tumor growth by targeting abnormal expression of protein kinase N3 (PKN3) expression, and using hyperthermia to kill prostate cancer cells.[150] Herein, we focus on the application of nanoparticles in immunotherapy.

Studies have been conducted on the clinical transformation of nanomedicine products in prostate cancer immunotherapy. Guo et al used PSMA aptamer (Apt)-functionalized putamen nanoparticles in paclitaxel (PTX)-resistant LNCaP (LNCaP/PTX) cells. The nanoparticles were found to inhibit epithelial–mesenchymal transition and re-sensitize cancer cells to PTX.[151] Mangiferin-functional gold nanoparticles (MGF-AuNPs) designed by Khoobchandani et al increase the expression of antitumor cytokines IL-12 and TNF-α by regulating the balance between pro-tumor M2 and antitumor M1 macrophages in mice with prostate cancer. It also reduces the expression of the tumor-promoting cytokines IL-10 and IL-6.[139] Meanwhile, Cole et al used cationic RALA/pDNA NPs combined with dissolvable microneedle patches to create a two-layer delivery system. This system effectively delivers a prostate cancer DNA vaccine to the dermal and epidermal APCs, enhancing the antitumor immune response and delaying tumor growth in mice with prostate cancer, ultimately prolonging survival.[152] Similarly, Islam et al activated the $CD8^+$ T-cell-mediated antitumor response using nanoparticles containing antigen-coding mRNA and TLR7/8 agonists.[153]

Translational Barriers

Although nanomedicine has considerable potential in prostate cancer immunotherapy, several translational barriers have hindered its clinical application.

1) Safety concerns: Nanomedicines have unique properties that, although beneficial, pose potential safety concerns. Understanding the long-term effects and toxicity of nanoparticles remains a major challenge.[154]
2) Scalability: Producing nanomedicines on a scale suitable for widespread clinical use is complex and expensive. Therefore, it is important to ensure consistency in quality and efficacy across batches.[155]
3) Regulatory approval: The novelty of nanomedicines complicates the regulatory approval process. Demonstrating their safety and efficacy, as well as establishing their superiority over existing therapies, are critical factors for regulatory approval.[9]
4) Patient stratification: It is important to determine which patients will benefit the most from nanomedicine-based treatments. This requires the selection of patients using biomarkers and monitoring their treatment response.[156]

Strategies to Overcome Translational Barriers

Several strategies have been proposed to address translational barriers and promote the clinical application of nanomedicine in prostate cancer immunotherapy.

1) Increased safety through design: The development of nanoparticles with biocompatible and biodegradable materials can minimize toxicity and improve safety. A targeting component can also be added to reduce off-target effects.[157]
2) Improve scalability using advanced manufacturing technology: Advances in manufacturing technology using nanotechnology can improve scalability and reduce costs. Continuous manufacturing processes and automation can provide this solution.[158]
3) Navigating the regulatory pathway: Engaging with regulators early in the development process can address regulatory challenges. Establishing clear guidelines for evaluating nanomedicines could streamline this process.[62]
4) Advancing patient stratification: Investing in research to identify and validate patient-selected biomarkers is critical. Combining nanomedicine with precision medicine can help improve patient outcomes.[159]

Nanomedicine presents a groundbreaking opportunity for prostate cancer immunotherapy by offering targeted, effective, and less toxic treatment options. Overcoming translational barriers through innovative design, manufacturing application, regulatory strategies, and precision medicine approaches will be pivotal to realizing nanomedicine's full potential in clinical settings.

Future Directions and Innovations

The advancement of nanomedicine in the field of prostate cancer immunotherapy has been marked by the development of intelligent nanocarriers and stimulus-response systems. These innovative platforms are designed to improve the delivery and efficacy of immunotherapeutics by targeting the TME with high precision. Smart nanocarriers can be designed to identify specific tumor markers to ensure that therapeutic agents are delivered directly to cancer cells, minimizing systemic toxicity and improving patient outcomes.[58,59] The stimulus-response system further complements this approach by releasing therapeutic payloads in response to specific physiological triggers within the TME, such as pH changes or enzyme activity, providing a controllable, targeted therapy strategy.[60]

Smart Nanocarriers and Stimulus-Responsive Systems

Despite significant advancements in nanoscale drug delivery technology, the drug delivery efficacy of most conventional carriers remains limited by their single release curve, which remains unchanged over time and fails to adapt to the specific needs of patients or physiological environments.[160,161] Moreover, the effectiveness of nanoscale drug carriers is often compromised due to immune system defenses.[162] Therefore, the development of intelligent and controllable nanocarriers is imperative. These nanocarriers should not only exhibit flexible drug release in diverse environments but also deliver immunomodulators locally and effectively while minimizing side effects to enhance therapeutic outcomes. In addition, nanomaterials have diverse structures and can easily undergo functional modifications, providing opportunities for developing intelligent stimulus-responsive nanodrug delivery systems.[163] These smart nanocarriers flexibly release drugs in different environments and locally and effectively release immunomodulators while reducing side effects, improving therapeutic effectiveness.[164,165]

Future directions and innovations in prostate cancer immunotherapy should focus on the development of smart nanomedicine delivery systems that respond to specific physiological and pathological stimuli. Stimulus-responsive nanomaterials have been engineered to construct intelligent drug delivery systems that recognize distinct features of the TME, such as acidic pH, peroxide levels, and the presence of specific enzymes, enabling more precise drug delivery. In this way, the local concentration of immunotherapy drugs will be enhanced without corresponding increases in adverse effects on normal tissues. Moreover, the therapeutic effect by will be enhanced by modulating the immune response, providing a more personalized and effective treatment plan for patients with prostate cancer.

The responsiveness of intelligent nanomaterials to stimuli can be categorized into endogenous and exogenous stimuli, with the stimulus-response system further classified into single-stimulus-response and multi-stimulus-response nanosystems. Stimulus-responsive nanosystems can accurately release drugs upon exposure to specific stimuli, exhibiting exceptional specificity in response to various stimuli to modulate the immune system by releasing immunomodulators, thus improving cancer treatment.

Smart Nanocarrier Mechanisms

Smart nanosystems can regulate the immune system to improve cancer treatment through the following mechanisms:

1) Endogenous stimulus-response: Smart nanosystems can recognize specific markers in the TME, such as low pH and highly expressed enzymes or peroxide levels. For example, pH-sensitive nanocarriers dissociate in an acidic TME, releasing immune activators that directly activate the surrounding immune cells to enhance tumor attack.
2) Exogenous stimulus-response: Using external stimuli, such as light, magnetic fields, or ultrasound, smart nanosystems can release immunomodulators at specific times and locations. For example, light-sensitive nanocarriers offer a targeted approach to delivering immune enhancers directly to tumors through irradiation with near-infrared light, minimizing systemic side effects and enhancing treatment specificity.
3) Multi-stimulus-response systems: By integrating endogenous and exogenous stimulus responses, multi-stimulus-response nanosystems enable precise drug delivery under more complex regulatory conditions. Such systems can simultaneously respond to changes in the TME and external stimuli, facilitating the fine control of immunomodulator release to more effectively modulate the immune system and improve cancer treatment outcomes. Through

these mechanisms, smart nanomaterials can improve the efficiency and specificity of drug delivery while also effectively activating or suppressing immune responses by precisely controlling the release of immunomodulators. This innovative treatment is expected to significantly improve treatment outcomes for cancers, including prostate cancer, providing patients with more personalized and effective treatment options.

These stimulus-response systems can specifically react to various stimuli, including the redox environment,[166] pH,[167] heat,[168] light stimulation,[169] magnetic fields,[170] enzymes,[171] ultrasonic stimulation,[170] etc., and can release immunomodulators at specific sites. However, stimulus-response systems with synergistic effects between multiple stimuli are more likely to deliver and release immunomodulators effectively.[172,173] Immunomodulators encompass various substances capable of modulating immune responses, including cytokines, chemical factors, small-molecule drugs, and specific proteins. In prostate cancer immunotherapy, the precise release of immunomodulators is essential for activating or inhibiting specific immune pathways to enhance the therapeutic effect or reduce adverse reactions. For example, pH-sensitive nanocarriers can release immune activators such as cancer vaccines or long-acting cytokines in the acidic TME, directly activating T cells and natural killer cells to generate a strong immune response against tumor cells. Simultaneously, nanosystems that respond to heat or light stimulation can be used to remotely control the release of anti-inflammatory cytokines or immunosuppressants to mitigate immune-related side effects that may occur during treatment. Furthermore, multi-stimulus-response nanosystems can detect multiple environmental signals, such as simultaneous responses to the properties of drugs and pH changes in the TME, enabling more precise and selective immunomodulator release strategies. This system ensures that immunomodulators are released when and where they are most needed, maximizing the effectiveness of the treatment and minimizing the impact on normal tissues. Therefore, the development of intelligent nanocarriers capable of responding to single or multiple physiological and pathological stimuli for the precise delivery and release of immunomodulators provides new strategies and directions for the design of immunotherapeutics for complex diseases such as prostate cancer.

Various novel multi-stimulus-response nanosystems have been designed. Researchers have designed smart size/shape convertible nanomedicines that can respond to near-infrared laser irradiation and an acidic TME, effectively ablating tumors and inhibiting metastasis. Nanomaterials can inhibit the mobility of tumor cells and significantly prolong the residence time of MEL/Cypate@HA in tumor tissues, achieving effective tumor clearance.[174] Furthermore, an HA-functionalized nanoparticle platform based on molybdenum disulfide responds to near-infrared laser irradiation and a reoxidation environment, achieving targeted delivery of CPT. This platform not only prevents random leakage of encapsulated CPT into the bloodstream but also accelerates drug release in tumor-associated environments rich in glutathione (GSH). MoS2-SS-HA-CPT effectively inhibits the proliferation of lung cancer cells and tumor growth under near-infrared irradiation.[175] Meanwhile, tunable nanocapsules have been developed that are able to respond to near-infrared laser irradiation and the TME. These nanocapsules are coated with Fe/FeO core-shell nanocrystals in a PLGA-polymer matrix and co-loaded with chemotherapeutic drugs and photothermic agents. These cleverly designed nanocapsules not only shrink and decompose into small-sized nanoscale drugs upon drug release but also regulate the TME to produce excess ROS, enhancing the synergistic treatment of tumors.[176] Other studies have used near-infrared dyes (eg, IR820) as carriers to induce the supramolecular assembly of chemical drugs (eg, Docetaxel, DTX) to form nanoparticles with enhanced drug-coating properties. These nanoparticles exhibit a dual response to MMP and GSH. NP-coated NIR dyes can be used as photothermal conversion agents for effective photothermal therapy. In addition, a CF27 peptide containing 12 D-amino acid units was designed as a PD-L1 agonist to block the immune checkpoint PD-1/PD-L1 interaction.[177] This peptide was encapsulated within cancer cell membrane mesoporous organosilica nanoparticles (MONs) that possess X-ray and room-responsive diselenide bonds. Additionally, these MONs were loaded with doxorubicin within pinhole diselenide-bridged structures and coated with membrane segments from cancer cells to facilitate tumor targeting and evasion of the immune system.[178] Additionally, pH/ROS cascade prodrug micelles have been developed with size-shrinking and charge-reversal properties. These micelles can deliver siTGF-β, leading to synergistic TME remodeling.[179] Similarly, novel nanomaterials with dual pH and redox responsiveness have been designed to enhance therapeutic efficacy in prostate cancer treatment.

Through their unique immunomodulatory mechanisms, nanomaterials can activate or regulate the immune system's response to tumors, enhancing the immunotherapeutic effect. For example, DNA-based nanomaterials are widely used in innovative and effective cancer immunotherapy, including for the delivery of ICD inducers, adjuvants, vaccines, and immune checkpoint blockers, as well as applications in immune cell engineering and adoptive cell therapy. These nanoplatforms can precisely deliver immunomodulators capable of triggering specific responses in immune cells, such as enhancing T-cell activity or modulating the immunosuppressive environment. In the field of prostate cancer treatment, pegylated manganese-zinc ferrite nanocrystals combined with tumor-implanted micromagnets enable synergistic prostate cancer therapy through the activation of iron death and ICD, a strategy that further amplifies the effects of ICD by stimulating the cGAS–STING pathway. Therefore, combining the immunomodulatory mechanisms of these nanomaterials with specific applications in prostate cancer treatment has the potential to improve treatment outcomes while also providing patients with more personalized and effective treatment options. Future research should focus on exploring the specific mechanisms of these nanomaterials in prostate cancer immunotherapy and on how to achieve personalized cancer immunotherapy by designing smarter nanomedicines.

New Strategies for Prostate Cancer Immunotherapy

ZIF-8@DOX @organosilica nanoparticles (ZDOS NPs) demonstrate significant potential for exploring new strategies in prostate cancer immunotherapy. These nanocores, with nanoscale ZIF-8 cores and silicone shells containing disulfide bonds, provide a good structure and up to 41.2% doxorubicin loading capacity also helping to activate immune responses.[180]

ZIF-8 nanoparticles can induce endogenous pyroptosis via a caspase-1/gasdermin D (GSDMD)-dependent pathway, accompanied by necrosis and ICD, providing a new pathway for effective in situ immune initiation. Moreover, delivering PD-1 inhibitors via ZIF-8 nanoparticles demonstrates a precise and targeted approach to cancer therapy, reducing non-targeted effects and enhancing therapeutic efficacy. This combination strategy addresses the existing challenges and limitations of current immunotherapy technologies, with the ultimate goal of improving patient outcomes in cancer treatment. Notably, in the context of prostate cancer treatment, the application of ZDOS NPs extends beyond simply increasing drug loading. More importantly, these nanoparticles hold the potential to regulate the TME, facilitate immune cell penetration, and stimulate the immune response. For example, by altering the pore size and surface properties of ZIF-8 nanoparticles, controlled drug release can be achieved to activate an immune response against prostate cancer cells while reducing damage to healthy tissues. Therefore, the application of ZDOS NPs in prostate cancer immunotherapy not only reflects their function as drug carriers but also their unique value in activating and regulating the immune system.

Personalized Nanomedicine: A Vision for Prostate Cancer Immunotherapy

The ultimate goal of advancements in nanomedicine is to establish a personalized approach for prostate cancer immunotherapy that tailors treatments to the genetic makeup, tumor characteristics, and immune profile of an individual patient. This approach fully exploits the potential of nanotechnology, artificial intelligence, and machine learning to design highly specific nanocarriers that can effectively target and regulate the TME, enhance immune responses against cancer cells, and overcome resistance mechanisms. The promise of personalized nanomedicine lies in its ability to provide more effective, less toxic, and highly specific treatment regimens, thereby changing the landscape of prostate cancer immunotherapy.[181–183]

Recently, a concept known as personalized nanomedicine has emerged, combining precision medicine and nanomedicine. This approach involves integrating a patient's omics information, including their genome, metabolome, and proteomics data, with nanotechnology.[184] This integration enables the development of more precise treatment plans tailored to individual patients. Compared with a one-size-fits-all approach, a precision medicine approach may help more accurately predict which treatment and prevention strategies will be effective for a particular patient population. Precision medicine refers to the medical diagnosis, treatment, and products tailored to individual patients.[184,185] However, designing personalized nanomedicine presents challenges due to the overexpression of specific metabolic enzymes in patients, which can prematurely degrade the matrix and targeted ligands. Additionally, many targeted ligands do not correspond to the most overexpressed cell surface receptors in cancer.

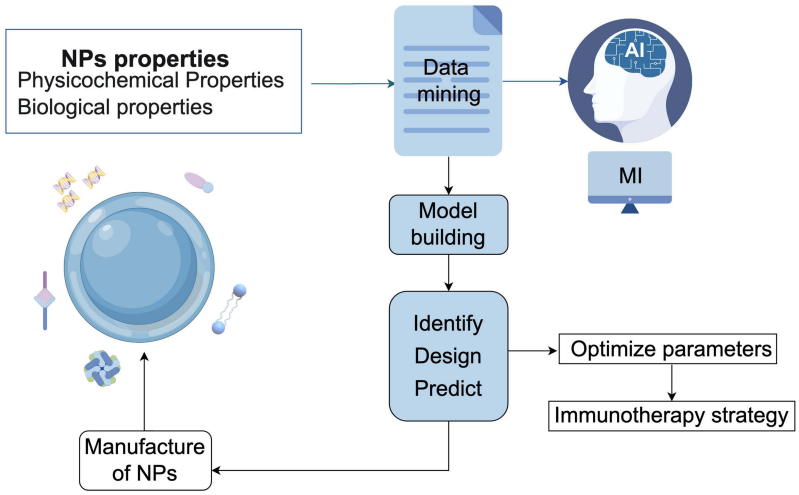


Figure 4 Using databases and AI to design nanomaterials for immune response and immunotherapy.

Recent research demonstrates that combining nanotechnology platforms with cancer immunotherapy strategies enables precise regulation of prostate cancer treatment. For example, the use of ZIF-8 nanoparticles as carriers of PD-1 inhibitors improves the efficiency of targeted drug delivery and enhances the effect of immunotherapy by regulating the TME. In addition, nanotechnology can activate the immune system to attack tumors by regulating the immunosuppressive state in the TME, improving therapeutic effects.

Artificial Intelligence (AI) and Machine Learning in Nanomedicine Design

The integration of AI and machine learning (ML) in the design and optimization of nanomedicines for cancer immunotherapy is a frontier research area (Figure 4 by Figdraw). These technologies offer an unprecedented ability to analyze complex biological data, predict nanocarrier behavior, and optimize treatment outcomes. AI and ML algorithms have been successfully used to identify new biomarkers, design personalized nanomedicine formulations, predict patient responses to immunotherapy, and create more effective and personalized treatment plans.[186,187]

Through AI, it is possible to optimize the drug and dose parameters of nanomedicine drugs. Indeed, AI has been utilized in diagnostics, therapeutics, personalized drug targeting and dosing, and the assessment of nanotoxicity in nanomaterials (Table 4).

Table 4 Application of AI/MI in Nanomedicine

Application fields	Description	Methods	References
Diagnostic application of AI	Nanopore sequencing technology	Single-molecule real-time (SMRT) sequencing approach	[188,189]
	Intelligent nanosensors for biomarker profiling	A quantum dots-based ultrasensitive nanosensor detect a point mutation of the KRAS gene; a nanotube-CTC chip; magnetic nanotechnologies for lipid biopsies; a giant magnetoresistance (GMR) biosensor with a capability of detecting twelve tumor biomarkers;	[190–193]
Therapeutic application of AI	AI in nanomedicine for achieving therapeutic synergism	Polymer@Gef-YAP-siRNA NPs; quadratic phenotypic optimization platform (QPOP), identify optimized drug combinations for specific patients; CURATE.AI optimize combination therapies for prostate cancer	[194–197]

(*Continued*)

Table 4 (Continued).

Application fields	Description	Methods	References
AI in nanomedicine design for personalized drug targeting and dosing	Drug loading and release process	All-atom molecular dynamics (AAMD), coarse- grained molecular dynamics (CGMD), dissipative particle dynamics (DPD), Monte Carlo (MC) and theoretical methods.	[198]
	The penetration of phospholipid bilayer membrane	Coarse-grained (CG) models	[199]
	Self-assembly	Molecular dynamics (MD) and CG	[200]
	Drug distribution	MD simulations	[201]
	Drug retention	MD simulations	[202]
	Evaluate direct interactions between nanoparticles and cells.	Metropolis Monte Carlo; ML-based algorithm	[203,204]
	Predict personalized drug potency	A high throughput system to detect DNA barcode	[205,206]
Application of AI in nanotoxicity	Predict the toxicity of nanomaterials	A genetic algorithm-tuned support vector machine classifier (GA-SVMC) model	[207]
	The nanotoxicity of a carbon nanotube	Quantitative structure–property (or activity) relationships (QSPR)	[208]

This involves determining the appropriate degree of drug exposure required to achieve the optimal therapeutic effect, reducing time and dose dependence. Additionally, AI can facilitate personalized treatment by adapting to the specific needs of each patient.[209] The application of AI is not limited to the optimal combination of a single drug but also includes real-time adjustments during treatment to respond to changes in the TME and dynamic changes in the patient's immune status.

The application of AI in nanomedicine facilitates drug dose optimization and combination therapy strategies by identifying powerful drug combinations within a vast parameter space. Clinical treatment studies across various cancers have demonstrated the effectiveness of this approach. Patients exhibit considerable variability in the required drug doses to achieve synergistic effects and optimal treatment outcomes. Moreover, these parameters can fluctuate over time within the same patient. The emergence of AI is poised to play a pivotal role in reconciling these complexities, enabling the development of more effective and safer treatments in nanomedicine.[210,211]

Conclusion

Nanomedicine represents a pivotal advancement for improving prostate cancer immunotherapy. It encompasses diverse delivery platforms, each offering unique advantages in this context. Nanotechnology is expected to overcome many limitations of immunotherapy, such as immune escape and the challenges of TME regulation. Nanotechnology can also enhance the delivery efficiency and therapeutic effectiveness of checkpoint inhibitors, cancer vaccines, and T-cell therapies to overcome various limitations of immunotherapy. Integrating nanomedicine with traditional treatments like chemotherapy and radiotherapy has shown promise in achieving superior outcomes compared to standalone therapies, fostering synergistic effects in combination therapy. This multifaceted approach improves drug bioavailability, enhances tumor targeting, and minimizes side effects, thereby advancing prostate cancer diagnosis and treatment. While clinical translation may face hurdles such as safety, scalability, regulatory approval, and patient stratification of nanomaterials, ongoing research and the integration of advanced technologies such as AI and ML in both research and clinical settings offer promising avenues for addressing these challenges. We advocate

for continued innovation and exploration in this dynamic field to unlock the full potential of nanomedicine in prostate cancer immunotherapy.

Funding

This work was supported by the WU JIEPING MEDICAL FOUNDATION (No. 320.6750.2023-11-34).

Disclosure

The authors report no conflicts of interest in this work.

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