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Review Article

Potential prospects of nanomaterials in bladder cancer treatment

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ABSTRACT

Treatment options for malignancies of the urinary system have improved with the introduction of nanotechnology and nanomaterials. Drug delivery vehicles can be employed with nanoparticles. On malignant cells, several nanoparticles have inherent therapeutic properties. Clinicians are concerned about malignant tumors with a high degree of medication resistance and poor patient prognosis. Treatment outcomes may be enhanced by using nanomaterials and related technologies to combat malignancies of the urinary system. Many advancements have been achieved recently in using nanomaterials to treat bladder cancer malignancies. The treatment of bladder cancer has evolved with the developing science of nanomedicine. Nanomedicine offers a promising path toward enhancing bladder cancer therapy by minimizing the major adverse effects, boosting tumor inhibition, and overcoming the resistance associated with conventional neoplastic medication. This review offers fresh suggestions for further research on nanotechnologies in this area. It covers the most recent findings on the application of nanomaterials in the diagnosis and management of malignancies of bladder cancer.

Keywords: *nanomaterials; malignancy; bladder cancer; treatment.*

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1. Introduction

Bladder cancer (BC) is considered the tenth most frequent cancer in the world **[1]**, with gradually increasing incidence **[2]**. It is more prevalent in men and the elderly **[3]**. Around 75% of bladder cancer patients suffer from non-muscle invasive bladder cancer (NMIBC), whereas 25% are involved with muscle-invasive bladder cancer. The prognosis of non-muscle-invasive bladder cancer leads to lethal muscle-invasive bladder cancer. The most significant modifiable risk factor for bladder cancer is tobacco use, which is responsible for around half of all cases, as well as genetic predisposition, chronic bladder inflammation, persistent bladder infections, and occupational exposure to certain toxins, chemicals, or dyes **[4]**. The management of bladder cancer tumors is varied and requires early detection for better outcomes. The treatment modalities of bladder cancer include systemic chemotherapy, intravesical therapy, gene therapy, immunotherapy, combined therapy, radical cystectomy, transurethral resection of bladder tumor (TURBT), and surgery. The primary treatment for non-muscle-invasive bladder cancer is TURBT **[5]**. Chemotherapeutic agents are intravesically instilled to act as

adjuvants post-surgery to avoid recurrence.

The bladder permeability barrier (BPB), which exists on the uroepithelial surface, influences medication penetration, normal bladder emptying, and drug dilution and causes several unbearable adverse effects that include drug resistance, short retention time, low drug permeability, minimized reaction time, and fast release, which remain unsolved problems during the course treatment of systemic chemotherapy **[6]**. Gene therapy is directed to replace the denatured nucleic acid by expressing functional ones in the cell to alleviate the symptoms associated with bladder cancer. The most significant struggle associated with gene therapy is the lack of a substantial host **[7]**.

Immunotherapy has become a viable strategy for the treatment of bladder cancer by raising the patient's immune response toward the target cancer cells **[8]**. There are some adverse effects associated with immunotherapy related to the patients' immunity, like the immunity dynamic disturbance and immunotoxicity due to the perfusion of high concentrations of immunity cells. Photodynamic therapy is one of the best selective bladder cancer therapies that target the tumor cells through an external light inducer that stimulates photosensitizers to produce reactive oxygen species (ROS) that trigger apoptosis and keep the normal status of the healthy tissues.

Managing bladder cancer entails meticulous monitoring to identify any recurrence or metastasis **[9]**. Direct visualization of the bladder is carried out using X-ray films, ultrasonography, magnetic resonance imaging (MRI), and computed tomography (CT) scans **[10, 11]**. Establishing individualized surveillance plans and selecting suitable routine therapy for each patient are dependent on their history, tumor features, definite type, stage of bladder cancer, degree of metastasis, and general health. The basic goal of bladder cancer management is to eradicate the tumor and prevent recurrence or progression while preserving bladder function. The treatment of BC has evolved with the developing science of nanomedicine **[12]**. There are various benefits of using nanoscale carriers, such as nanoparticles (NPs), to carry the anticancer agents directly to the tumor cells as compared to traditional chemotherapy **[13, 14]**. Nanomedicine offers a promising path toward enhancing bladder cancer therapy by minimizing the major adverse effects and boosting tumor inhibition. Overcoming the resistance associated with conventional neoplastic medications is one of the most challenging prospects to overcome and this is carried out through increasing the selectivity toward the targeted bladder urothelial cells followed by enhancing cellular uptake and permeability that will lead to accumulation as well as increased extravasation. Moreover, the decrease in the drainage of nanoparticles by lymphoid tissues leads to a higher retention effect within the bladder urothelium which is responsible for an eventual amplified efficacy **[15]**. Nanoparticles act as excellent vehicles to ensure targeted and sustained release of drugs as well as enhancing the bioavailability and medication delivery, which raises the overall efficacy of the treatment. Furthermore, nanoparticles (NPs) can prolong the therapeutic residence period in the bladder, which enhances the anticancer efficacy **[16]**. Nanoparticles are an intriguing option in the realm of cancer therapy since the adsorption of certain selected peptides or induced antibodies to the surface can additionally improve the identification and selectivity of bladder cancer cells **[17-19]**. Nanomaterials are the most efficient carriers for the management and diagnosis of bladder cancer, as they exhibit exceptional features like large surface area, small size, strong reactivity, and quantum effect. They allow customized treatment according to the needs of every patient, improving therapy outcomes and reducing

emerging side effects. This review will first categorize the different types of nanoparticles. Next, we will examine the mechanisms by which these nanoparticles interact with bladder cancer cells. Finally, we will discuss the metabolism and toxicity of nanoparticles, including strategies for minimizing potential risks.

2. Types of nanocarriers

The biomedical industry has employed an expanding variety of medication delivery methods supported by nanocarriers in recent years. Different types of nanocarriers have been developed to address particular requirements in clinical research. Two primary types of nanoparticles are currently utilized in medication delivery systems that use nanocarriers: organic and inorganic. Liposomal and polymeric nanoparticles are examples of organic nanocarrier types; while magnetic, gold, and mesoporous silica nanoparticles are examples of inorganic nanocarrier types. **Table 1** provides a quick summary of the properties of the nanoparticles used to treat bladder cancer, and **Fig. 1** shows the different types of nanocarriers.

Table 1. Summary of the properties of the nanoparticles (NP) used to treat bladder cancer

Nanoparticle	Advantages	Disadvantages	Applications	REF
Liposomes	High biocompatibility, nontoxic, nonimmunogenic, great bioavailability and adaptability, easy surface modification and good protection of loaded medicines	Poor stability, low drug loading, easy leakage, prompt clearance, off-target accumulation, and high-price	Drug delivery, increased drug stability, noninvasive imaging, drug targeting, and gene therapy	**[20] [21]**
Micelles	Excellent biocompatibility and biodegradation, drug targeting to tumor tissue, prolonged circulation time, ameliorate the accumulation and retention at the tumor site.	Poor stability and reduced drug encapsulation efficacy	Drug delivery system and bioimaging	**[22, 23]**
Nanogels	Strong biocompatibility and biodegradability, hydrophilicity, facile entrapment by the cells, excellent drug delivery capacity, and prolonged retention time	Prompt clearance, off-target accumulation, drug degradation, and drug release are difficult to control	Drug delivery system, gene therapy, regeneration medicine, and bioimaging guided treatment	**[24]**
Chitosan	Strong mucoadhesion, biocompatibility, biodegradability Low cytotoxicity and facile enzymatic solubility	Poor solubility at physiological PH and variation in the features of chitosan nanoparticles in the hemodynamic environment	Targeted drug delivery system, regeneration therapy, gene therapy, and tumor image-guided treatment	**[25, 26]**
Nanoemulsions	Enhanced bioavailability, better loading capacity, and improved skin penetration with minimum skin irritability	Poor solubility and thermodynamically instability	Targeted drug delivery system and bioimaging tool	**[27, 28]**

Metal-organic framework	Biocompatibility, large surface area with exceptional modification capacity, high tissue penetration, increased drug accumulation and targeted drug delivery ability	Cytotoxicity, organ toxicity, Poor thermal and chemical stability	Targeted drug delivery of chemotherapeutic agents, photodynamic photothermal, and multimodal imaging	**[29]**
Gold nanoparticles	Large surface area, superior conductivity high biocompatibility, easy entry into the host, feasible preparation, excellent surface modification and controllable size distribution	Cytotoxicity, organ toxicity, Neurotoxicity and difficulties of synthesis of stable nanoparticles	Drug delivery, photothermal therapy, radiation therapy, immunotherapy, enzyme fixation and cell imaging	**[30, 31]**
Magnetic nanoparticles	High biocompatibility, biodegradability, magnetothermal therapy effect and Superparamagnetism features	Cytotoxicity, Rapid agglomeration and high surface energy	Hyperthermia cancer treatment, controlled drug release, magnetic resonance imaging, biosensing, tumor imaging and radiotherapy	**[32, 33]**
Mesoporous silica nanoparticles (MSN)	High biocompatibility, adjustable particle size multifunctional surface, high loading capacity large surface area and pores volumes	Hard synthesis of uniform size distribution system, adsorption, and interaction with the cell membrane in vivo inducing hemolysis	Drug and gene delivery, MSN-assisted bioimaging, tissue regeneration, MSN based carriers and MSN-based biosensors	**[34, 35]**
Quantum dots	High photochemical stability, fluorescence quantum yield and biocompatibility	Contain heavy metals, organ toxicity, environmental pollution and immunotoxicity	Biomolecule targeting, luminescence Imaging and drug delivery	**[36]**

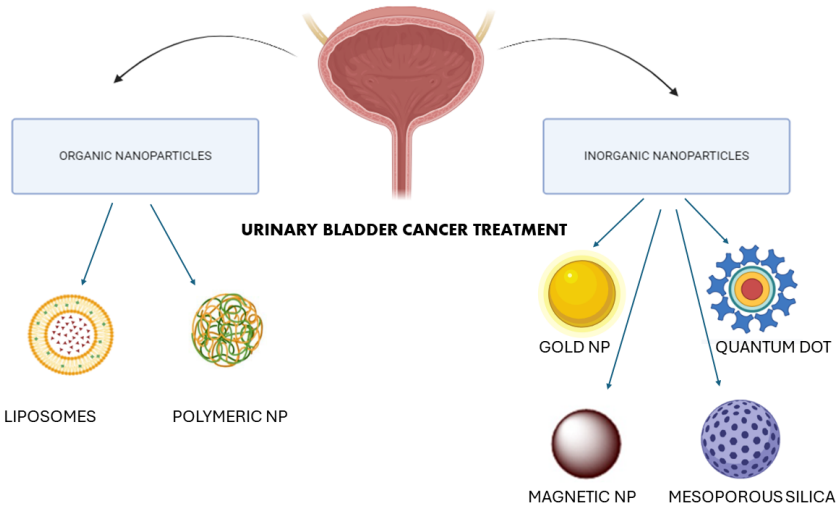

Fig. 1. Types of nanocarriers

2.1. Organic material nanoparticles

2.1.1. Liposomes

Liposome vesicles are lipid-mediated drug delivery systems **[37]**. They are well known for their biodegradability owing to their capabilities to dissolve hydrophilic as well as lipophilic moieties. The derivation from cholesterol and phospholipids demonstrates significant biocompatibility, high loading rate, relatively feasible synthesis, and stability, which enable them to be one of the best candidates for drug delivery **[38, 39]**. The release of the loaded drug is triggered by dynamic changes that may occur in the microenvironment of liposomes at a particular spot or regulate the intended release in the tissue **[40]**. There are six primary forms of liposomes: ligand-targeted liposomes, enzyme-triggered liposomes, pH-sensitive liposomes, ultrasound-sensitive liposomes, and enzyme-triggered liposomes **[41]**. Bladder cancer management entails the utilization of specific types of liposomes, which are mainly modified and ligand-targeted liposomes.

Doxil® is the first liposomal medication authorized by the US Food and Drug Administration (FDA) that contains the anticancer substance Adriamycin hydrochloride **[42]**. When compared to traditional intravenous (IV) therapy, the concentration and dispersion of Doxil® within liposomes in the bladder are substantially greater. It has been demonstrated that when anticancer medications are enclosed in PEGylated liposomes, there is an improvement in both distribution and protection against the opposed stomach environment **[43]**. A variety of medications (compounds) have been utilized to increase PEGylated liposome effectiveness for bladder cancer in vitro and in vivo. To sum up, PEGylated liposomes improve the activities of drugs and hold tremendous promise for developing into an effective anticancer delivery system to replace Doxil® in clinical settings. Although liposomes are excellent nanocarriers, they fail to achieve the optimum delivery efficiency, and they accumulate in sites away from the targeted ones.

One of the main applications of liposomes is the encapsulation of the Bacillus Calmette-Guérin vaccine (BCG) with specific ligands on top of the liposomes to permit cellular penetration. It is known that the primary immunological active center of the Mycobacterium Bacillus Calmette-Guérin vaccine (BCG) is its cell wall skeleton (BCG-CWS), which is a strong contender for non-infectious immunotherapeutic medication for the management of bladder cancer. BCG-CWS was nanoparticulated in methylene chloride and then encapsulated with conventional liposomes (CL) to formulate (CWS-Nano-CL) utilizing an emulsified lipid approach to enhance the internalization of BCG-CWS into bladder cancer cells without aggregating. As demonstrated by in vitro cell proliferation studies, CWS-Nano-CL outperformed nonenveloped BCG-CWS in inhibiting the development of bladder cancer cells. Encapsulated BCG-CWS nanoparticles may improve the luciferase-tagged mouse bladder tumor line-2 (MBT2) bladder cancer cells in an orthotopic implantation paradigm. BCG/CWS-modified liposomes are considered a potentially highly efficacious therapeutic candidate in bladder cancer **[44]**.

In another study, scientists designed a cation-based liposome that incorporates the mycolic acid to be uptaken by murine bladder cancer cell line (MB49) efficiently and therefore improve the in vivo antitumor activity **[45]**. Liposome-mediated drug delivery systems emerged as potential prospects in treating bladder cancer, with proven selected drug delivery ability and improved therapeutic effects.

In a different study, Zhai et al. **[46]** synthesized a special peptide-selected liposome

that encapsulated an amino-terminal segment with β-elemene adsorbed on the surface. This allowed the active compounds to directly reach the tumor cells' stimulator receptor of plasminogen urokinase which is highly expressed in those cells. The antineoplastic agent cisplatin was combined for efficient bladder cancer therapy. The receptor-mediated internalization enhanced the cellular drug distribution and therapeutic benefits of nanoparticle drug carriers.

Lv et al. **[47]** reported that the hyperthermia associated with phosphatidyl glycerol-mediated thermosensitive liposomes (DPPG-TSL) activated the release of the active compound and suppressed the toxicities of the conventional chemotherapeutic agents. DPPG-TSL showed great results in orthotopic murine models. Liposome vesicles carrying chemotherapeutic agents are the promising drug delivery host for the management of BC.

Ghaferi et al. **[48]** demonstrated the treatment efficacy of anticancer cisplatin conjugated to liposomes and liposomes coupled to polyethylene glycol in vitro and in vivo models as nanocomposites for the management of bladder cancer. The results revealed that the efficacy of liposomes had been enhanced upon conjugation with polyethylene glycol. PEGylated liposomes are a promising drug delivery system to prepare nanoformulations with developed antitumor effects and reduced cytotoxicity.

2.1.2. Polymeric nanoparticles

Polymers are supramolecular structures consisting of substantial large moieties **[49]**. Polymers-based drug delivery vehicles are featured with regulated drug release time, biocompatibility, and hydrophilic as well as lipophilic targeted release **[50]**. Active compounds could be loaded within the polymer molecules or adsorb onto the surface, and many chemotherapy drugs are conjugated on nanopolymeric hosts to enhance antitumor activity, inhibiting dissemination to other body parts and decreasing the effective dosage and adverse effects **[51]**. There are many classes of polymeric vehicles used for active compound delivery, such as gels, chitosan, microemulsions, and micelles.

Researchers were developing a polymeric nano vector that consisted of antitumor cisplatin conjugated to poly(l-aspartic acid sodium salt) (PAA) or methoxy-poly(ethylene glycol)-block-PAA (PEG-PAA) polymers. They tested the polymeric nanovector on animal models, and the results revealed that the polymer enhanced the targeted delivery and increased the survival of the murine models **[52]**. The drug activation cascade reduced the toxicity in normal cells and expanded the selectivity during intravesical bladder cancer (BC) chemotherapy. This system revealed a great avenue as a targeted drug delivery system (DDS) for BC management. During the course treatment of BC, a fluorinated polymer DDS emerged to improve drug penetration.

Research conducted by Li et al. **[53]** used a combined fluorinated polyethyleneimine (F-PEI) with chorion-e6-coupled catalase (CAT-Ce6) to facilitate the degeneration of bladder tumors through induction of hypoxia in the tumor tissues and applied it using in vivo modeling. The polymeric system demonstrated enhanced therapeutic efficacy with reduced systemic cytotoxicity, which showed great promise for treating bladder cancer.

Another study performed by Poinard et al. **[54]** demonstrated a lipophilic photosensitizer chlorin e6 loaded within the biopolymer polydopamine (PDA) nanoparticles to be applied for bladder anticancer drug delivery through maintaining the surface charge and hydrophilicity. This model was tested in vitro using the human bladder cancer cell line T24 to

check for cell viability and proliferation. The results revealed that this model exhibited strong colloidal stability, high drug loading capacity, and drug release over an extended time. It is considered a potential approach for effective cancer phototherapy.

Tan et al. **[55]** constructed a polymer-based drug delivery vehicle consisting of photosensitizer chlorin e6 and cathepsin B-sensitive polymer [oligoethylene glycol methacrylate (OEGMA)] for loading the antineoplastic agent paclitaxel (PTX). The polymeric nano host was assessed using in vivo models and resulted in a reduction in tumor proliferation and full eradication of bladder tumors. According to these findings, NPs@Ce6 could act as a prominent candidate for bladder cancer therapy.

2.1.2.1 Polymeric micelles

Micellar polymers are a special class of drug delivery carriers consisting of amphiphilic copolymers with hydrophobic and hydrophilic moieties that enable self-assembly into a core-shell composite **[56-58]**. The nanosized micelles ranged from 10 nm to 100 nm and are characterized by remarkable stability in the biological media. The hydrophobic core of the micelles solubilizes poorly soluble medicines, while the hydrophilic shell can shield the medication from breakdown and improve its pharmacokinetic characteristics. The prolonged release of medications and their extended circulation time in vivo compared to free drugs are made possible by polymeric micelles, which improve therapeutic effectiveness. Polymeric micelles exhibit great potential for targeted cancer therapy and are valuable tools for medication delivery.

Zhou et al. **[59]** constructed a micelle polymer-based drug delivery system loaded with the anticancer agent doxorubicin and consisted of a hydrophobic cyclic (RGDfK) peptide moiety adsorbed on surface-manipulated micelles and a hydrophilic moiety of poly(ε-caprolactone) (PCL)-b-poly(ethylene oxide) (PCL-b-PEO), which represents a unique class of block copolymers with many applications in the biomedical field. The constructed system was employed for in vitro testing, and the outcomes revealed higher efficiency against human bladder cancer cell line T24 and suppression of cell proliferation when conjugated with doxorubicin. Micellar polymers showed great promise as nanosystems intended for targeted drug delivery for bladder cancer management.

In another research study developed by Zhou et al. **[60]**, a system was composed of amphiphilic micelles polymer consisting of a hydrophilic segment of an amine group, PCL-b-PEO-NH_2, and loaded with a lipophilic segment of fatty acid and fluorescein isothiocyanate to be employed for in vitro testing. The findings demonstrated a strong affinity to the human bladder cancer cell line T24 with fatty acid with no inhibitory effect detected on 293 normal human embryonic kidney cells.

Another study constructed by Yu et al. **[61]** displayed a micellar system composed of polyethylene glycol and poly(*N*-(2-hydroxypropyl)methacrylamide) encapsulated with chemotherapeutic agent doxorubicin for in vitro assay. The outcomes depicted a significant effect in selecting and uptaking of the conjugates by bladder tumor cells, leading to greater cytotoxicity in comparison to free doxorubicin.

It was mentioned in another study by Zhu et al. **[62]** that researchers fabricated micellar-based nanocomposite consisting of internally cross-linked micelles poly(ethylene glycol) and poly(ε-caprolactone) with disulfide bond PEG-PCL-SS loaded with chemotherapeutic agent doxorubicin and a near-infrared dye IR780. The fabricated nanoformulation reacted to increased

concentrations of glutathione, which is highly expressed in bladder tumor cells, and near-infrared laser radiation. It is characterized by prolonged circulation and decreased cytotoxicity and can produce heat under near-infrared laser irradiation, which can further trigger drug release. The nanoparticle system was tested in vitro and in vivo for evaluation, leading to the remarkable outcomes of enhanced therapeutic efficacy of photothermal therapy and chemotherapy for the management of bladder cancer.

In another research study, Xu et al. **[63]** created micelles formed of poly(ethylene oxide)-block-poly(propylene oxide)-block-poly(ϵ-caprolactone) (PEO-PPO-PCL) that encapsulated the antineoplastic agent docetaxel efficiently along with the anti-inflammatory agent chloroquine inhibitor. The dual drug-loaded micelles polymer was assessed *in vitro* and in vivo to evaluate the cytotoxicity and cellular perfusion. The outcomes revealed that the micelle is safe to use with regulated extended-release duration and amplified accumulation in the tumor cells, which showed prospects for encapsulation with antineoplastic agents.

Lin et al. **[64]** prepared a cyclic peptide with the amino acid sequence cQDGRMGFc, known as PLZ4, which demonstrated the ability to attach to a special receptor that is highly expressed in the bladder cancer cells known as αVβ3 integrin in a specific manner. PLZ4 micelles were coupled to multifunctional nanoporphyrin complexes (PNPs) loaded with doxorubicin (Dox) for selective diagnostic and therapeutic purposes of bladder cancer. PLZ4 micelles with PNPs and Dox employed prolonged circulation time and extended drug release. Both in vitro and in vivo assessments were carried out, and the findings depicted that micelle nanoparticles loaded with the active compounds represent a functional and efficient strategy to realize the superior antitumor effect against bladder cancer.

A cationic micelle was developed by Jin et al. **[65]** when 1,2-dioleoyl-3-trimethylammonium propane/methoxy poly (ethylene glycol) was conjugated to doxorubicin and the nanocomposite was tested in vivo. The in vivo outcomes showed an amplified anti-cancer activity of doxorubicin compared to the free one in the management of bladder cancer. The nanocomposite employed enhanced endocytosis by the bladder endothelium and eventual substantial accumulation in the tumor site. The micelles showed great promise as nanocarriers for the neoplastic agents.

2.1.2.2. Gels

A hydrogel is one of the main types of organic polymers applied in the delivery of active compounds due to their simple synthesis, improved drug conjugation, and prolonged stability of the loaded drug for optimal use, besides their softness, flexibility, biocompatibility, and high tensile strength **[66]**. Nanogels are nanosized types of hydrogels **[67]**. Many stimuli are affecting the drug dose delivered by the polymeric nanogels, such as temperature and light. They enhance the therapeutic outcomes and decrease the adverse effects associated with the loaded drug **[68, 69]**. The nanogels have contributed to the development of regulated and extended-release drug delivery systems (DDS) **[68]**.

GUO et al. **[70]** fabricated an encapsulated nanogel system by synthesizing cationic cross-linked peptide nanogel and then conjugating 10-hydroxycamptothecin (HCPT) into the gel by simple diffusion. The constructed nanogel system was evaluated in vitro and in vivo. It demonstrated in vitro more cytotoxicity against human T24 bladder cancer cells than did free HCPT. Furthermore, in an orthotopic bladder cancer model, the cationic-loaded nanogel demonstrated markedly improved antitumor

activity and decreased adverse effects in vivo. Nanogels are considered one of the most promising drug delivery systems due to their high drug loading efficiency, sustained retention duration, enhanced tissue penetration capabilities, and the accurate and rapid release of HCPT in bladder cancer cells. Smart carriers of nano gels loaded with antineoplastic agents are the area of study to enable established multi-stimulus response systems for triggered drug release, which is vital for bladder cancer therapeutic and diagnostic purposes.

2.1.2.3. Chitosan

Chitosan is a naturally derived positively charged biopolymer scaffold with excellent mucoadhesive ability owing to the presence of functional groups that enable surface alterations of the targeted bound ligand. It is a non-toxic polymer with biocompatible and biodegradable features **[71, 72]**. Chitosan nanoparticles are widely used as efficient drug carriers for their successful applications in imaging, diagnostic, and therapeutic purposes **[73]**. They are considered to be an effective drug delivery system for cancer management that enables targeting of the cancer cells based on enhanced permeability in the tumor cells as well as extended retention time **[74]**.

Liu et al. **[75]** prepared optimized paclitaxel/chitosan nanoimplants and evaluated them in vitro and in vivo to check for cell viability profile as well as cellular proliferation. The chitosan-based nanoimplants displayed high paclitaxel loading efficiency, extended-release duration, and increased mucosal adhesion features. The experimental outcomes specified low cytotoxicity and high antitumor effect; hence, it was considered to be a potential candidate for bladder cancer management. Nanoparticles with effective and improved surface modifications are a promising field of interest.

In another research study, Ay Şenyiğit et al. **[76]** developed an optimized nanoformulation of chitosan-based drug delivery system coated with thioglycolic acid and fully loaded with anticancer gemcitabine HCL and conducted in vitro and in vivo evaluation. The findings revealed that the optimized nanoformulation exhibited long-term retention time as well as amplified efficacy of gemcitabine HCL in treating bladder cancer.

It was specified in a study performed by Wang et al. **[77]** that encapsulation of conventional anticancer agents' cisplatin and doxorubicin with the cationic nanocarrier chitosan coated with poly methacrylic acid offered a promising path for other traditional antineoplastic agents to be incorporated to overcome all the adverse effects and the drug resistance. The synergistic polymeric nanocomposites exhibit characteristic prolonged residence duration and effective delivery to the bladder tissues.

Ghoshal et al. **[78]** designed a nanoformulation using chitosan and alginate in gold nanoclusters (Au NCs) that are attached to a bacterially expressed human recombinant secreted frizzled protein 1 (sFRP1). The sustained release of sFRP1 outside the cell is enabled by these nanoparticles (NPs). Additionally, the remarkable luminescent properties of Au NCs are utilized for binding, imaging, and tracking studies. The therapy entails the synergistic use of sFRP1-loaded NPs and the drug cisplatin, which targets two distinct pathways to induce apoptosis through a combination of their individual effects.

Burjak et al. **[79]** prepared a surface-modified chitosan nanocarrier with 2 carried substrates which were NAD(P)H quinone oxidoreductase 1 known as the NQO1 substrate and a serine/threonine protein kinase inhibitor known as the KP372-1 substrate, which encapsulated the antineoplastic agent epirubicin to investigate the cellular uptake extent and the

eventual efficacy against the bladder cancer cells. The nanoformulation was assessed in vitro to check for cell viability and proliferation. The cationic chitosan results demonstrated exceptional mucoadhesive capabilities and permeability to the bladder cell wall to deliver the nanoformulation to the target tumor cells. The active drug Epirubicin was stimulated by the carried substrate NQO1, while the substrate KP372-1 was responsible for the activation of reactive oxygen species within the bladder urothelial cells. The delivery system showed reduced cytotoxicity to normal cells through a selective inhibitory effect on the bladder cancer cells **[80]**.

It was reported in another research study done by Sun et al. **[81]** that fluorinated chitosan-based nanoparticles loaded with the chemotherapeutic agent paclitaxel and H_2 catalyst can produce H_2 under laser irradiation effectively, enhancing the efficacy of hydrogen-based chemotherapeutic agents against bladder cancer in vitro and in vivo. The nanocomposite showed a controlled paclitaxel release, enhanced permeability, as well as a complete inhibition of tumor proliferation and hence an eventual amplified antineoplastic efficacy and reduced adverse effects accompanied with the conventional treatment of paclitaxel.

A study conducted by Martin et al. **[82]** to detect the therapeutic effect of cationic chitosan nanoparticle-based delivery host formulated from poly(lactic-co-glycolic acid; PLGA) encapsulating the therapeutic survivin RNA (siRNA) for bladder intravesical instillation. The system was evaluated in vitro and in vivo using a murine model. The in vitro findings revealed an extended therapeutic effect and a significant reduction in cell proliferation compared to blank chitosan nanoparticles without SiRNA. The in vivo results displayed a major decrease in bladder tumors compared to the blank chitosan nanoparticles.

The research was done by Liang et al. **[83]** to demonstrate the efficiency of a chitosan-based delivery vector to target the CD 44 receptor highly expressed in bladder cancer patients through a specialized survivin RNA (siRNA) encapsulated with hyaluronic acid dialdehyde in an ethanol-water combination to be attached to the chitosan nanoparticles. The model was evaluated in vitro and in vivo. The results depict enhanced stability, increased siRNA conjugation capacity, and minimized cytotoxicity. The nano delivery system targeted the CD44 receptor efficiently, delivered the therapeutic siRNA into T24 bladder cancer cells, and hampered the apoptosis inhibitor gene Bcl_2 in the in vivo model of bladder cancer. **Table 2** summarizes different chitosan-based nanoformulations.

Table 2. Different chitosan based nanoformulations

Drugs	Chitosan nanoconjugates	The synthesis methodology of Nanoparticles	The outcomes	Ref.
Bacillus Calmette—Guerin (BCG)	BCG-loaded chitosan nanoparticles	ionotropic gelation technique	In a rat model, BCG-loaded chitosan nanoparticles led to a longer life period (up to 86 days of survival without systemic adverse effects) than BCG commercial products.	**[84]**
Mitomycin C (MMC)	MMC-loaded chitosan nanoparticles	ionotropic gelation technique	Greater interactions between cells and mucosa enable longer retention periods of nanoparticle formulations in the bladder.	**[85]**
Cisplatin & Doxorubicin (Dox)	chitosan–polymethacrylic acid (CM) nanocapsules	Chitosan and methacrylic acid (MAA) chains undergoing polymerization interact electrostatically.	In ex vivo research, the CM-Dox-PtALy nanocapsule demonstrated sustained drug delivery properties and noteworthy synergistic effects.	**[86]**

2.1.2.4. Microemulsions

Microemulsions are a special type of polymeric vectors consisting of oil, water, surfactant, and co-surfactant that are thermodynamically stable **[87]**. It offers major advantages that include regulated drug release as well as improved drug stability **[88]**. Nanoemulsions, despite being thermodynamically unstable, can solubilize drugs of low bioavailability, enhancing the drug retention time **[89, 90]**. Co-surfactants presented in microemulsions play a crucial role in creating a flexible and dynamic layer by lowering the surfactant film's tension, improving the drug's dispersion, and facilitating simple transdermal absorption **[74]**. Nanoemulsions are better than microemulsions as they deliver the full dose to the target sites. Nanoemulsions can interact directly with the tumor tissues for a prolonged time as they escape the mononuclear phagocytic system (MPS) and the renal clearance **[91]**.

In a study, Chen et al. **[92]** employed microemulsions as drug delivery carriers to raise the perfusion efficacy of the antineoplastic agent's gemcitabine and cisplatin in a dual-loading manner into the bladder endothelium, leading to boosting their synergistic antitumor effects. The dual synergistic-loaded microemulsion was assessed using an in vivo model. The results confirmed that microemulsions will be one of the best drug delivery systems, especially for IV admixture of antineoplastic drugs.

2.1.2.5. Metal-organic frameworks

Metal-organic frameworks (MOFs) are a kind of high-porosity crystal consisting of organic substrates, metals, and metal clusters. They exhibit unique physicochemical properties like adjustable pore size, prominent surface area, well-defined pore volume, and easy surface alteration. All these factors contribute to formulating potential drug delivery vectors that enable the best biocompatibility and drug permeability **[93, 94]**.

Chen et al. **[95]** developed a nanocarrier named HAFeR, which conjugated [inhibitors of glutathione peroxidase 4 (GPX4)] and inducers of cellular death within MOFs known as PSs and RSL3. HAFeR was able to identify the highly expressed CD44 receptor on the bladder tumor cell surface and was phagocytosed by the receptors of the neoplastic cells to release the iron ions, which induce hypoxia in the bladder tissues through generating reactive oxygen species (ROS). The nanoformulation was evaluated in vitro and in vivo using murine cancer cell line MB49. The findings revealed that HAFeR displayed high cytotoxicity and complete tumor ablation of the MB49 in the tumor model.

Huihui et al. **[96]** prepared a MOF-derived nanocarrier system composed of a human MOF called KAT8 loaded with the antineoplastic agent gemcitabine. In vitro assessment was conducted to evaluate the cytotoxicity of the model and check for cell viability and proliferation using the human bladder cancer cell line T24. The outcomes showed a synergistic effect between gemcitabine and MOF to inhibit the proliferation and the metastasis of rapidly divided cells of the bladder tumor and enhance apoptosis.

Li et al. **[97]** developed a newly optimized bacterial system coated with a protective Zeolitic imidazolate framework-8 (ZIF-8) MOF and loaded with antineoplastic agent doxorubicin. The targeted nanocomposite offers new perspectives to enhance the drug delivery capabilities, extend the residence time, increase the attachment to the bladder endothelium, and eventually achieve the highest therapeutic outcomes in treating bladder cancer.

2.2. Inorganic material nanocarriers

2.2.1. Gold nanoparticles

One of the main types of nanoparticles is gold nanoparticles (AuNPs) which possess many outstanding properties like prominent surface area-to-volume ratio, prolonged stability, ease of synthesis, multifunctionality, surface plasmon resonance (SPR), and exceptional surface chemistry **[98, 99]**. They are non-toxic and non-immunogenic, and they display high biocompatibility and permeability, as well as prolonged retention time, which facilitates the drug accumulation at the bladder tumor. Their special characteristics allow them to become the most potential tools for diagnostics and drug delivery applications **[100]** through their unique optical and SPR features **[101]**.

It was aimed at research conducted by Daei et al. **[102]** to study the anticancer activity of gold nanoparticles (AuNPs) against bladder cancer and evaluate the cytotoxicity in vitro and in vivo. They found that there was an inhibitory effect of AuNPs induced in 5637 bladder cancer viable cells treated with different concentrations of AuNPs after 24 h and decreased the survival rate of 5637 cells in a dose-dependent manner. These AuNPs stimulated the apoptosis of tumor cells by increasing the expression of the proapoptotic protein Bax, reducing the oncogene Bcl-2 that is highly expressed in the bladder tumor, and raising the production of reactive oxygen species (ROS) within the cells. Gold nanomaterials exhibit a powerful photothermal activity that assists in overcoming the bladder mucosal barrier and acts as potential carriers for drug delivery.

Wang et al. **[103]** used glutathione as a template to create radiant gold nanoparticles (Au NPs) that were subsequently sealed with a silicon dioxide (SiO_2) shell to increase their biocompatibility. Au@SiO_2@Au nanoparticles were then developed by depositing gold nanoclusters on the surface of the nanoparticles, and then 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride was applied to link hyaluronic acid (HA) in the nanoformulation of Au@SiO2@Au to target cancer cells highly expressing CD44 receptors to facilitate the attachment of nanoparticles and subsequently increase the accumulation in tumors. Both *in vitro* and *in vivo* testing were applied, and the results revealed improved treatment outcomes through full eradication of the bladder tumor with no common recurrence seen.

Hsu et al. **[104]** synthesized a folic acid (FA) conjugated with both gold nanoparticles and tannic acid Au@TNA loaded with methylene blue to induce photodynamic therapy (PDT) in bladder cancer cells through the accumulation of small photosensitizers. The nanocomposite was tested in vitro to check for cell viability against human cancer cell line T24 and cytotoxicity induced within the cells, which resulted in the reduction of cell viability in a dose-dependent manner. Experimental outcomes revealed that this safe photomedicine has great potential to achieve targeted elimination of bladder tumors without significant adverse effects.

Liao et al. **[105]** developed a nanoformulation of gold nanoparticles (AuNPs) encapsulated with a natural photosensitizer, iron chlorophyllin, and evaluated the cytotoxicity *in vitro* using the human cancer cell line T24 and *in vivo* using mice-bearing bladder cancer. The results revealed an outstanding response of complete tumor ablation without recurrence detected.

2.2.2. Magnetic nanoparticles

Magnetic materials with particle sizes ranging from nanometers to micrometers are intriguing for use in biological and medical applications in addition to magnetic recording

[106-108]. Their exceptional characteristics, which include their high surface area to volume ratio, excellent surface chemistry, multifunctionality, and simplicity of synthesis, make them the ideal option for drug release, drug carrier, and cancer therapy **[109]**. They possess a superparamagnetic behavior and high saturation magnetization in response to magnetic fields. Magnetite nanoparticles (MNPs) are thought to be the most studied nanomaterials. They are also thought to be non-toxic, highly biocompatible, and non-immunogenic, and their high permeability and retention effect show additional benefits by facilitating drug penetration and accumulation at tumor sites **[107, 110]**.

Magnetic nanoconjugates loaded with bioactive drugs offer the advantage of extended circulation in the bloodstream and substantial minimization of cytotoxicity of therapeutic agents. They are the future's most promising diagnostic and therapeutic tools. One of the main pros of MNPs is their capability to be magnetically modulated by an outer magnetic field **[111]**. MNPs can modify the pharmacokinetics of the bioactive drugs to minimize cytotoxicity and improve the drug release rate. Moreover, MNPs can be altered by using high-affinity substrates, and applying an external magnetic field will assist in localizing MNPs to cancer cells. Magnetic nanoparticles are commonly used upon conjugation with antineoplastic agents. They have been successfully implemented in drug selection strategies to raise the profile level of drug accumulation and effectiveness in bladder cancer management. There are various magnetic drug vectors designed and applied to deliver different types of anticancer agents.

Tao et al. **[112]** fabricated a nanoformulation consisting of polydopamine coated with magnetite nanoparticles (Fe_3O_4) with modified folic acid fully loaded with the anticancer agent vincristine and conducted in vivo testing. The outcomes showed a complete eradication of the bladder tumor with improved colloidal stability, increased biocompatibility of the nanocomposite, and extended systemic circulation time owing to the presence of polydopamine. The magnetic nanoparticle vectors showed a potential prospect in treating Bladder cancer.

Sun et al. **[113]** designed a magnetic thermosensitive hydrogel using magnetic iron oxide nanoparticles that act as an innovative delivery system for intravesical instillation of Bacillus Calmette Guerin vaccine (BCG), allowing a prolonged retention time in the bladder through magnetic field surveillance. The hydrogel increased the permeability into the bladder endothelium through a whole solidification process into a gel and sticking to the bladder wall. The hydrogel displayed strong anti-tumor effects in bladder cancer due to its sustained release and targeting features.

Qi et al. **[114]** also developed a special magnetic mucoadhesive hydrogel encapsulated with iron oxide nanoparticles for intravesical delivery and coated with hyaluronic acid to overcome the chemotherapy-resistant bladder cancer through a three-stepwise sustained delivery strategy to the targeted tumor cells. Compared to systemic administration, this novel three-stepwise strategy delivery of iron oxide nanoparticles, resulting in an up to 50-fold increase in iron content, facilitated the ferroptosis reaction, which eventually allowed a recurrence-free state of disease and promoted the therapeutic outcomes.

In another study, SUO et al. **[115]** established a study to compare the conventional antineoplastic agent Epothilone in the free form and the encapsulated form carried by magnetic nanoparticles for effective intravenous instillation in BC treatment. A magnetic multi-walled carbon nanotube was synthesized, loaded with

Epothilone, and coated with magnetite (Fe_3O_4) nanoparticles for in vitro and in vivo evaluation. The outcomes revealed that the synthesized nanocomposite was safe for use. The prepared nanoformulation showed improved cytotoxicity results besides the antiproliferative efficiency in vitro and in vivo compared to the free form of Epothilone for potential clinical application.

In another research, Huang et al. **[116]** constructed a magnetic polymer-based nanoparticles system that employed poly(ε-caprolactone)-b-poly(propargyl methacrylate-click-mercaptosuccinic acid-co-poly(ethylene glycol) methyl ether methacrylate) (PCL-b-P(PMA-click-MSA-co-PEGMA)) loaded with the antineoplastic agent cisplatin and encapsulating the superparamagnetic iron oxide nanoparticles for effective bladder cancer treatment and evaluated it in vitro using bladder cancer cell line UMUC3. The findings revealed a slow, extended-release of cisplatin over days. Furthermore, the nanoformulation induced remarkable cytotoxicity against the bladder cancer cell line UMUC3. The magnetic nanoparticle-based nanocomposites loaded with cisplatin are potentially useful for bladder cancer treatment.

Wang et al. **[117]** synthesized a new functional nanocomposite consisting of magnetite (Fe_3O_4) as the source of magnetic properties and doxorubicin-loaded calcium phosphate (CaP) and coated with alginate. Fe_3O_4/CaP/alginate was evaluated using in vitro testing to check for cell viability against the human cancer cell line T24. The outcomes showed that the magnetic nanocomposites turned into a gel upon phagocytosis by the bladder tumor cells, which subsequently improved the mucoadhesion in the bladder endothelium for enhanced therapeutic outcomes of T24 cells under magnetic effect to give a great future promise for drug delivery by magnetic nanoparticle vectors.

Chin et al. **[118]** fabricated a nanoformulation consisting of magnetite (Fe_3O_4) loaded with iron chlorophyll photosensitizer (iron oxide@chlorophyll) cluster nanoparticles encapsulated with 4-carboxyphenylboronic acid and evaluated it in vitro to check for cell proliferation. The results showed that reactive oxygen species produced (ROS) from the photosensitizer induced apoptosis within the tumor tissues and eventually increased the associated cytotoxicity for better therapeutic effects, which opened a new horizon for enhancing the efficacy of the conventional anticancer agents.

In another research study, Lin et al. **[119]** designed a nanostructured formulation that provides oxygen to escape hypoxia commonly occurring in patients suffering from bladder cancer. The cyclic peptide PLZ4 with the amino acid code of cQDGRMGFc, was used coupled with an organoselenium ion and conjugated with magnetic iron oxide nanoparticles (PLZ4@SeD) for effective targeted intravesical instillation. This nanosized oxygen provider is a potential treatment for hypoxic resistance cases in bladder cancer patients.

2.2.3. Mesoporous silica

Mesoporous silica nanoparticles (MSN) are the best nanocarriers known for their simple preparation, stability, and biocompatibility features **[120, 121]**. MSN employs unique features that enable it to deliver drugs, such as a high surface area and pore volume, tunable particle and pore sizes, and variable morphology. This is in addition to their capacity to produce core-shell particles with unique surface functionalization, which improves the likelihood of being efficient nanocarriers. The mesoporous silica possesses a surface structure that is easily manipulated by various triggering recipients, selecting agents and ligands, thus extending the circulation time of the drug **[122]**. Although

mesoporous silica nanoparticles have undergone extensive research for their prospective application as drug delivery systems and in cancer management, they are not widely applied clinically due to their high-cost expenses.

Zhang et al. **[123]** constructed a well-developed modified mesoporous silica nanoparticle (MSN) for drug loading by introducing β-cyclodextrin moiety and fluorocarbon moiety loaded with anti-tumor drug doxorubicin (Dox). MSN-Dox was evaluated in vitro and in vivo for potential cytotoxicity. The outcomes showed improved mucosal adhesion to the bladder endothelium besides the biodegradability, slow enhanced drug release process, and reduced adverse effects of conventional antineoplastic agent doxorubicin.

Wei et al. **[124]** fabricated multifunctional mesoporous silica nanoparticles (MSN) coated with polydopamine (PDA) and conjugated with CSNRDARRC peptide (PEP) and loaded with the anticancer agent doxorubicin (Dox) for an effective targeted bladder cancer treatment. The anticancer efficacy of the multifunctional Dox-loaded MSN-PDA-PEP was assessed in vitro using the MTT assay and in vivo using a murine model, demonstrating that the fabricated selected nanocarrier showed a significantly superior effect compared to free Dox and can be used for substantial selected bladder cancer management.

Wang et al. **[125]** developed a new modified mesoporous silica nanoparticle (MSN) by attaching poly(amidoamine) (PAMAM) and examined the mucoadhesive capability in vivo using a pig bladder. The results displayed an amplified mucoadhesive ability for prominent intravesical instillation. The antineoplastic agent doxorubicin was loaded onto the MSN surface nanocarrier, which resulted in a targeted mucoadhesive drug delivery system for an effective bladder cancer treatment.

Hortelao et al. **[126]** created a special surface-modified mesoporous silica nanoparticles (MSN) nanosphere composed of anti-fibroblast growth factor receptor 3 (FGFR3) antibody and polyethylene glycol. The phagocytosis of MSN nanocomposite by the urothelial cells was urea substrate-dependent for highly targeted therapeutic efficiency. The targeted therapy resulted in increased suppression of tumor cell proliferation to show future promise as selective bladder tumor management.

Haddick et al. **[127]** prepared a multisized MSN sequence ranging between 60 nm and 160 nm to encapsulate anti-tumor microRNA (miRNA). The multisized MSN nanocarrier was evaluated in vitro to check for cell proliferation, and the results showed ameliorated cellular uptake by the human bladder cancer cell line T24. MSN exhibited remarkable potential for hosting microRNA as a biocompatible nucleic acid delivery agent for effective bladder cancer treatment.

A current study reported by Shahidi et al. **[128]** revealed the potential utilization of MSN-conjugated siRNA/miRNA for an effective bladder cancer therapy. This nanocarrier was fabricated using cyclic peptide [c(RGDfK)] linked to poly(lactide-coglycolide) (PLGA)-poly(ethylene glycol) (PEG) modified for co-delivery of tumor suppressor microRNA (miR-34a) and programmed cell death-ligand 1 (PD-L1) siRNA. The designed system was assessed in vitro using the bladder cancer cell line T24 and in vivo using a murine model. The research displayed the biocompatible nanocarrier in the serum media and its role in protecting the therapeutic molecules from serum degeneration. Moreover, the c(RGDfK)-MSN was capable of upregulating miR-34a and PD-L1 expression, resulting in amplified antitumor effects in bladder cancer management. These outcomes emphasize the promising use of mesoporous silica as a

selected delivery agents for nucleic acids and its contribution when bound to specific ligands to enhance bladder cancer therapy.

Borzecka et al. **[129]** formulated new silica of different geometries conjugated with 2 types of photosensitizers: PS1 consisting of (4-10-thio-glucosyl-2,3,5,6-tetrafluorophenyl)porphyrin (SGlc-Por, PS1) and PS2 consisting of 5,10,15,20-tetrakis (4-10-thio-galactosyl2,3,5,6-tetrafluorophenyl)porphyrin (SGal-Por, PS2) and compared the results using 2 *in vitro* models of cancer cell lines, which represent the epithelial cell linings of bladder urothelial carcinoma HT-1376 and UM-UC-3. The results revealed that the intracellular endocytosis by the bladder cells for PS2 was better than PS1. The UM-UC-3 cancer line showed significantly higher uptake results and eventual phototoxicity compared to HT-1376 cancer cells. The optimized silica represents a major potential as an effective vector for delivering PSs into tumor tissues. Their findings demonstrated the potential of this PS targeting bladder cancer cells for photothermal therapy. It's interesting to note that in cancer cell lines, the mesoporous silica nanoparticles showed increased phototoxicity and singlet oxygen production. These outcomes implied that this new spherical nanosystem would work well as a bladder cancer photodynamic candidate.

A novel strategy was adopted by Sweeney et al. **[130]**, which entailed creating mesoporous silica with a specific bladder cancer cell peptide, Cyc6. The fabricated mesoporous silica along with Cyc6 were tested in vitro and in vivo using a murine model. The cyc6-modified mesoporous silica confirmed improved selectivity for bladder cancer. The cyc6 functionalized mesoporous silica could be used as a potential drug delivery system for antineoplastic agents. Further studies should be applied to human clinical trials for drug administration, therapeutic monitoring, and drug staging. This technique presented a viable way to target accurately the non-invasive BC, which could lead to better clinical results.

2.2.4. Quantum dot

Quantum dots (QDs) are specific types of nanomaterials that exhibit special physical and chemical characteristics, such as high stability and safety, which allow them to serve as one of the best drug delivery systems **[131, 132]**. QDs are smart functional delivery systems to be widely applied for cancer management owing to their immense stability and adjustable emission.

Yuan et al. **[133]** designed a Quantum dot (QD) delivery vehicle bound to a prostate stem cell antigen (PSCA) conjugated with a monoclonal antibody (QD-PSCA) for inhibition of proliferation of bladder urothelial cancer cells in vitro and in vivo. The QD-PSCA fluorescent probe was characterized by superior optical stability, which facilitates imaging, early diagnosis, and bladder cancer management *in vivo*. One of the main limitations of *in vivo* application of fluorescent nanoparticles is the cytotoxicity detected following the systemic administration.

Pan et al. **[134]** examined the cytotoxicity and biodistribution of intravesical instillation of QD-PSCA fluorescent probe in mice, revealing that no significant accumulation of QDs was observed outside the bladder but was spotted in some extravesical biodistributions. For this reason, targeted nanoparticles with regulated biosafety measures were developed to minimize long-term toxicity in clinical settings and reduce systemic exposure. QDs have become useful instruments for biological study.

Manan et al. **[135]** fabricated a quantum dot-based delivery system that used Mn-doped zinc sulfide (Mn: ZnS) conjugated with cationic chitosan and loaded with the anticancer drug mitomycin C for efficient bladder cancer treatment. The proposed system is a viable

therapy option for non-muscle invasive bladder cancer as it can minimize the recurrence of cancer due to its improved drug loading capacity, increased bioavailability, targeted delivery to a tumor site, and extended retention time, which will eventually accomplish the best therapeutic response toward bladder cancer.

Isaac et al. **[136]** used quantum dot delivery agents to carry nano horns made of one carbon wall encapsulated with the anticancer drug cisplatin to tumor cells. The modified hybrid system serves perfectly as a chemotherapy delivery vehicle, as it shows outstanding results in preventing the proliferation of bladder cancer cells. This study presented the creation of the first carbon nanohorn, a combination of cisplatin as a chemotherapeutic payload with QDs for bladder cancer management.

Table 3 summarizes the current applications of nanotechnology in bladder cancer treatment.

Table 3. Current nanotechnology-based treatment for bladder cancer

Therapeutic type	Therapeutic agent	Material	Pros	Assessment	Ref
Chemotherapy	Doxorubicin	Gelatin-coated single-walled carbon nanotube	Improved targeted therapeutic efficacy and lower the cytotoxicity associated with the adverse effects of the drug	*In vitro* and *in vivo*	**[152]**
			Selective and improved drug therapy efficacy, PH sensitivity, and low adverse side effects		
			Enhanced targeted efficacy and temperature sensitivity		
	Doxorubicin	DOX-loaded MSN@PDA-PEP	Enhanced drug retention, permeability, and cellular entrapment	*In vitro* and *in vivo*	**[124]**
			Enhanced mucus adhesion to the bladder wall		
	Doxorubicin	LTD, ThermoDoxR@	Enhanced targeted efficacy of PTX by modifying the pharmacokinetic properties following the Iv infusion		**[153]**
	Doxorubicin	Dox/DPP micelles	Improved mucoadhesive ability in the bladder wall	*In vivo*	**[65]**
			Dual targeting and mucosal permeability		
	Doxorubicin	MSNG0~MSN -G3	Apoptosis and autophagy are caused by the selective suppression of bladder cancer cell proliferation at certain doses and the activation of the ROS/ERK signaling pathway.	*In vitro*	**[125]**
	Paclitaxel	Disulfide-crosslinked PLZ4-nano micelle (DC-PNM)	Improved mucosal adherence and penetration	*In vitro*	
			Triggering apoptosis of tumor cells and suppressing		

		tumor growth and dissemination in vivo		**[154]**
Paclitaxel	PTX/CS NSs	Suppression of in situ tumor cells without recurrence with no toxicity-induced		**[75]**
Gemcitabine	R11@TM@PLGAG	Stable chemical and physical features and minimal drug irritability enhancing the effectiveness of antioxidant cytotoxic medications and decreasing the spread of bladder cancer cells resistant to CDDP	*In vivo* *In vitro* and *in vivo*	**[155]**
Gemcitabine	CONPs		*In vitro*	**[156]**
10-Hydroxycamptothecin (HCPT)	R9NG/HCPT		*In vitro*	**[157]**
Mitomycin C (MMC)	MMC NPs		*In vivo*	**[158]**
Gambogic acid (GA)	Cationic chitosan		*In vitro* and *in vivo*	**[159]**
Cisplatin and gemcitabine	Gel-based microemulsions		*In vitro* and *in vivo*	**[92]**
Cisplatin	SiNrf2-GCD		*In vitro* and *in vivo* *In vitro*	**[160]**

Gene therapy	Paclitaxel and survivin siRNA	Polymer	Excellent encapsulation efficacy leading to full oligonucleotide transfection and blocking the surviving expression	*In vitro*	**[161]**
			Effective encapsulation and targeted drug delivery		
	Si-circRNAs or circRNAs	Synthesized chrysotile nanotubes (SCNTs)	Effective prevention of endosomal deterioration and quick cytoplasmic absorption of therapeutic siRNAs Bladder cancer is the spotlight of multicomponent siRNA/miRNA-loaded modified mesoporous silica nanoparticles, a highly successful combination treatment.	*In vitro* and *in vivo*	**[162]**
	siSPAG5	FeSiNTs		*In vivo*	**[163]**
	miR-34a and siPD-L1	c(RGDfK)-MSN NPs		*In vitro* and *in vivo*	**[128]**
Immunotherapy	Bacillus Calmette-Guerin cell wall skeleton	Liposome	Apoptosis is triggered in vitro and in vivo	*In vitro* and *in vivo*	**[44]**
	AB680 and aPDL1	AB680 @EMVs-aPDL1	Combined immunotherapy with multidrug delivery Amplification Of immunotherapy	*In vitro* and *in vivo*	**[164]**
	ICG and αPD-L1	MPDIαW	increasing the synthesis of interferon, triggering the activation of the atypical pathway, and improving the TLR4 pathway's (TLR4, TRIF, and IRF3) immune responsiveness	*In vitro* and *in vivo*	**[165]**
	P14 16 and CFI-1	OncoTherad® (MRB-CFI-1)		*In vivo*	**[166]**
	Immunotherapeutic oligonucleotide, CpG	RWFV-targeted LNPs	Combining pH-sensitive characteristics with specific ligands for immunotherapy	*In vitro*	**[167]**
	Listeriolysin O(LLO)	GNP-LLO91–99 nanovaccines		*Human study*	**[168]**

Combination therapy	Glucose oxidase and polypyrrole	GOx@ MBSA-PPy-MnO2 NPs	Combining PTT with glutathione (GSH)- and glucose-triggered chemodynamic treatment (CDT) to relieve hypoxia	*In vitro* and *in vivo*	**[169]**
			Treatment with synergistic chemotherapy and phototherapy is accomplished.		
			Tissue penetration and cell uptake are aided by good biocompatibility, an extended tumor tissue passivation accumulation cycle, and a short radiation-induced PCI effect.		
					[62]
	IR780 and DOX	DOX&IR780 @PEG-PCL-SS NPs		*In vitro* and *in vivo*	
					[55]
	Ce6 and paclitaxel	NPs@Ce6	reduction of harm to side-branch healthy tissue delivery of medications and focused heating to cancerous tissue	*In vitro* and *in vivo*	
	Doxorubicin, Gemcitabine, NIR	RGD-Au@Fe-MOF system (RAMOFs)	Chemotherapy and photothermal treatment together have minimal side effects and good synergistic therapeutic results.	*In vitro* and *in vivo*	**[170]**
	Doxorubicin, NIR	CS/PNIPAAm@SWCNTs		*In vivo*	**[171]**

3. Metabolism and toxicity of nanoparticles

Despite the major therapeutic efficiency of nanomaterials, cytotoxicity as well as pharmacokinetic metabolism should be studied. The dispersion of nanomaterials varies depending on their size, porosity, shape, and surface functionalization **[137]**. While a smaller particle size can increase a nanoparticle's penetration ability, particles smaller than 10 nm are quickly eliminated and unable to enter a tissue. Furthermore, by altering the ligand, nanoparticles' permeability into tissues can be increased. As a result, in designing nanoparticles, the demands of the body should be considered while choosing the proper size **[15]**. The shape of mesoporous silica affects the metabolism degree, whereas the spherical ones recorded the highest cytotoxicity, causing a severe reduction in the biodegradability, systemic absorption, and excretion, while the cytotoxicity associated with long rod-shaped nanoparticles was the least. The spleen and liver are the 2 main sites for mesoporous silica nanoparticles **[138]**. Gold nanoparticles possessing rod shape have less penetration and are promptly eliminated from the body than spherical and star-shaped nanoparticles, which accumulate for a longer time in the body. The star-shaped nanoparticles accumulate in the lung, while the spherical ones accumulate in the liver **[15]**. Gold nanoparticles are primarily concentrated in the liver, spleen, and bone marrow **[139]**. Quantum dot nanocontainers are extensively accumulated in the reticuloendothelial system and kidney. The movement of drug-loaded nanoparticles from the

bloodstream to tissues, intercellular fluid, and cells is referred to as distribution. Following absorption, blood circulation distributes nanoparticles throughout the body's tissues **[140]**. The distribution of nanoparticles may be influenced by many factors, such as blood flow, vascular permeability, plasma protein concentration, complement system, mononuclear phagocytic system, and interactions between nanoparticles and tissue cells **[141]**. Nanoparticles are promptly transported from the systemic circulation to the bone marrow, liver, and spleen, where they are finally collected **[142]**. Traditional nanoparticles accumulate in the liver with a percentage of 30–90% **[143]**. Both the spleen and liver become overabundant with nanoparticles, which affect the biosafety and the efficiency of drug delivery.

Biodistribution differs according to cytotoxicity-induced metabolism and biomedical applications. In terms of pharmacokinetic effect, firstly, the kidney and biliary tract are responsible for the clearance of nanomaterials, such as MSN and AuNP.

Hepatocytes are involved in the excretion of bile, which is responsible for the elimination of nanoparticles and their bound ligands. Kupffer cells exclusively rely on the breakdown of nanoparticles in cells to achieve elimination without contributing to the bile excretion. Hepatobiliary excretion is slower than renal clearance, taking time from hours to months. However, specific ligand modification can allow hepatocytes to absorb nanoparticles that neither the kidneys nor macrophages can eliminate **[144]**.

Secondly, nanomaterial metabolic rate depends on their size. The smaller nanomaterials are easier to metabolize than larger ones, like small gold nanoparticles (less than 10 nm) that showed better metabolism than larger ones **[145]**. Larger particle-size QDs are more difficult to remove and stay unaltered in vivo for extended periods. Thus, these nanomaterials can be engulfed by Kupffer cells presented in the liver and B cells found in the spleen. The nanoparticles with larger particle sizes (more than 10 nm) were able to skip clearance through glomeruli and were excreted in the urine.

Finally, the excretion route for nano molecules outside the body after endocytosis by the macrophages is presented in the alveoli **[146]**. There are many factors affecting the cytotoxicity of the nanomaterials, like particle size, the applied dose, the characteristic shape of each nanomaterial used, the presence of bioligand on the surface, and the surface functionalization **[147]**. The cationic nanoparticles with positive charges are more likely to induce immune response and cytotoxicity than neutral or negatively charged nanoparticles **[148-150]**. Kidney failure may result from nanoparticle metabolites that are eliminated by the kidneys due to their accumulation. Additionally, some substances, such as poloxamers and derivatives of cyclodextrin, have the potential to be toxic and result in renal impairment **[151]**.

Conclusion

The development of nanotechnology and nanomaterials for the diagnosis and treatment of bladder cancer has accomplished many successful results. Many of these concepts have not been applied to clinical practice. Many of these investigations are still in the experimental stage. Diagnostic and treatment methodologies are continuously evolving for patients suffering from bladder cancer tumors.

Before these new advancements were implemented in clinical settings, there were still several unresolved issues about nanoparticles. First, is there a way to increase the nanoparticles' targeting efficiency? Increased efficiency suggests that toxicity can be reduced by using lower dosages. Second, and perhaps most

importantly, is the question of how to lessen the adverse consequences of nanoparticles, which often result in liver and kidney damage. Third, simplifying the more high-throughput bulk manufacturing technique of nanoparticles to bring down their cost for large applications in clinical holding is necessary. Lastly, the trash generated during the creation of these nanoparticles has the potential to contaminate the environment; therefore, the production method should be altered to reduce this risk. More clinical research is required in light of the previously identified problems.

In addition, it is currently unclear if certain patient variables (such as age, sex, tumor kind, location, and prior therapy) would influence how certain nanoparticles work. Furthermore, it's unclear if nanoparticles might cause other illnesses, including diabetes and asthma, to flare up suddenly. Lastly, the trash generated during the creation of these nanoparticles has the potential to contaminate the environment; therefore, the production method should be altered to reduce this risk.

Ultimately, the majority of current research focuses on creating, manufacturing, and directing nanoparticles for tumor treatment. Novel clinical studies, such as the localization of nanoparticles, which is particularly important for tumor therapy, could be more advantageous for patients in terms of long-term anticancer benefits. Nanoparticle research is only getting started, and the majority of them have not yet been used in a therapeutic setting. Further clinical research will be necessary to ensure efficacy and safety. While several studies have demonstrated the benefits of using nanoparticles for therapeutic and diagnostic purposes, it is still important to keep an eye on their cytotoxicity and biosafety. Regular modification of nanoparticles is necessary to obtain the optimal structure that permits meaningful results.

Declarations

Ethics Approval and Consent to Participate

Not applicable

Consent to Publish

Not applicable.

Availability of Data and Materials

All data generated and analyzed in this study are included in the main published article and this manuscript.

Competing Interests

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Authors' Contributions

The manuscript was drafted and written by Alyaa Atef and Ghadir S. El-Housseiny.

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4. References

1. Ferlay J, Soerjomataram I, Znaor A, Jemal A, Bray FJEu. Bladder cancer incidence and mortality: a gl. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. 2021;71(3):209-49.
2. Siegel RL, Miller KD, Jemal AJCacjfc. Cancer statistics, 2019. 2019;69(1):7-34.
3. Antoni S,obal overview and recent trends. 2017;71(1):96-108.
4. Cumberbatch MGK, Jubber I, Black PC,

Esperto F, Figueroa JD, Kamat AM, et al. Epidemiology of bladder cancer: a systematic review and contemporary update of risk factors in 2018. 2018;74(6):784-95.

5. Sun X, Dai T, Xu LJFiS. Transurethral resection of bladder tumor-based bladder preservation therapy for refractory high risk non-muscle invasive bladder cancer: Current landscape and future directions. 2023;10:1143219.
6. Jafari NV, Rohn JLJMI. The urothelium: a multi-faceted barrier against a harsh environment. 2022;15(6):1127-42.
7. Wang S, Jin S, Shu Q, Wu SJP. Strategies to get drugs across bladder penetrating barriers for improving bladder cancer therapy. 2021;13(2):166.
8. Sweis RF, Spranger S, Bao R, Paner GP, Stadler WM, Steinberg G, et al. Molecular drivers of the non–T-cell-inflamed tumor microenvironment in urothelial bladder cancer. 2016;4(7):563-8.
9. Batista R, Vinagre N, Meireles S, Vinagre J, Prazeres H, Leão R, et al. Biomarkers for bladder cancer diagnosis and surveillance: a comprehensive review. 2020;10(1):39.
10. Panebianco V, Narumi Y, Altun E, Bochner BH, Efstathiou JA, Hafeez S, et al. Multiparametric magnetic resonance imaging for bladder cancer: development of VI-RADS (Vesical Imaging-Reporting And Data System). 2018;74(3):294-306.
11. Nicola R, Pecoraro M, Lucciola S, Reis RBd, Narumi Y, Panebianco V, et al. VI-RADS score system-A primer for urologists. 2022;48(4):609-22.
12. Barani M, Hosseinikhah SM, Rahdar A, Farhoudi L, Arshad R, Cucchiarini M, et al. Nanotechnology in bladder cancer: diagnosis and treatment. 2021;13(9):2214.
13. Davis A, Gao R, Navin NJBeBA-RoC. Tumor evolution: Linear, branching, neutral or punctuated? 2017;1867(2):151-61.
14. Chen J, Jiang Z, Zhang YS, Ding J, Chen XJAPR. Smart transformable nanoparticles for enhanced tumor theranostics. 2021;8(4).
15. Zhang A, Meng K, Liu Y, Pan Y, Qu W, Chen D, et al. Absorption, distribution, metabolism, and excretion of nanocarriers in vivo and their influences. 2020;284:102261.
16. Ashrafizadeh M, Zarrabi A, Karimi-Maleh H, Taheriazam A, Mirzaei S, Hashemi M, et al. (Nano) platforms in bladder cancer therapy: Challenges and opportunities. 2023;8(1):e10353.
17. Torchilin VPJNrDd. Multifunctional, stimuli-sensitive nanoparticulate systems for drug delivery. 2014;13(11):813-27.
18. Qiu H, Guo H, Li D, Hou Y, Kuang T, Ding JJTib. Intravesical hydrogels as drug reservoirs. 2020;38(6):579-83.
19. Guo H, Li F, Xu W, Chen J, Hou Y, Wang C, et al. Mucoadhesive cationic polypeptide nanogel with enhanced penetration for efficient intravesical chemotherapy of bladder cancer. 2018;5(6):1800004.
20. De Leo V, Maurelli AM, Giotta L, Catucci LJC, Biointerfaces SB. Liposomes containing nanoparticles: preparation and applications. 2022;218:112737.
21. Kim E-M, Jeong H-JJCmj. Liposomes: biomedical applications. 2021;57(1):27.
22. Tawfik SM, Azizov S, Elmasry MR, Sharipov M, Lee Y-IJN. Recent advances in nanomicelles delivery systems. 2020;11(1):70.
23. Majumder N, G Das N, Das SKJTd. Polymeric micelles for anticancer drug delivery. 2020;11(10):613-35.

24. Rajput R, Narkhede J, Naik JJA, DMPK. Nanogels as nanocarriers for drug delivery: A review. 2020;8(1):1-15.

25. Sivanesan I, Gopal J, Muthu M, Shin J, Mari S, Oh JJP. Green synthesized chitosan/chitosan nanoforms/nanocomposites for drug delivery applications. 2021;13(14):2256.

26. Yu S, Xu X, Feng J, Liu M, Hu KJIjop. Chitosan and chitosan coating nanoparticles for the treatment of brain disease. 2019;560:282-93.

27. Souto EB, Cano A, Martins-Gomes C, Coutinho TE, Zielińska A, Silva AMJB. Microemulsions and nanoemulsions in skin drug delivery. 2022;9(4):158.

28. Rehman AU, Anton N, Bou S, Schild J, Messaddeq N, Vandamme T, et al. Tunable functionalization of nano-emulsions using amphiphilic polymers. 2021;17(7):1788-95.

29. Hou Y, Zhu C, Ban G, Shen Z, Liang Y, Chen K, et al. Advancements and Challenges in the Application of Metal-Organic Framework (MOF) Nanocomposites for Tumor Diagnosis and Treatment. 2024:6295-317.

30. D'Acunto M, Cioni P, Gabellieri E, Presciuttini GJN. Exploiting gold nanoparticles for diagnosis and cancer treatments. 2021;32(19):192001.

31. Kumari Y, Kaur G, Kumar R, Singh SK, Gulati M, Khursheed R, et al. Gold nanoparticles: New routes across old boundaries. 2019;274:102037.

32. Khan AU, Chen L, Ge GJICC. Recent development for biomedical applications of magnetic nanoparticles. 2021;134:108995.

33. Popescu RC, Andronescu E, Vasile BSJN. Recent advances in magnetite nanoparticle functionalization for nanomedicine. 2019;9(12):1791.

34. Rastegari E, Hsiao Y-J, Lai W-Y, Lai Y-H, Yang T-C, Chen S-J, et al. An update on mesoporous silica nanoparticle applications in nanomedicine. 2021;13(7):1067.

35. Mohamed Isa ED, Ahmad H, Abdul Rahman MB, Gill MRJP. Progress in mesoporous silica nanoparticles as drug delivery agents for cancer treatment. 2021;13(2):152.

36. Bruno JGJAoQDiB, Advances MR. Advantages and disadvantages of using quantum dots in lateral flow and other biological assay formats. 2022:91-102.

37. Yan W, Leung SS, To KKJN. Updates on the use of liposomes for active tumor targeting in cancer therapy. 2020;15(3):303-18.

38. Wang G, Wu B, Li Q, Chen S, Jin X, Liu Y, et al. Active transportation of liposome enhances tumor accumulation, penetration, and therapeutic efficacy. 2020;16(44):2004172.

39. Šturm L, Poklar Ulrih NJIjoms. Basic methods for preparation of liposomes and studying their interactions with different compounds, with the emphasis on polyphenols. 2021;22(12):6547.

40. Li M, Du C, Guo N, Teng Y, Meng X, Sun H, et al. Composition design and medical application of liposomes. 2019;164:640-53.

41. Moosavian SA, Bianconi V, Pirro M, Sahebkar A, editors. Challenges and pitfalls in the development of liposomal delivery systems for cancer therapy. Seminars in cancer biology; 2021: Elsevier.

42. Li F, Qin Y, Lee J, Liao H, Wang N, Davis TP, et al. Stimuli-responsive nano-

assemblies for remotely controlled drug delivery. 2020;322:566-92.

43. Taher M, Susanti D, Haris MS, Rushdan AA, Widodo RT, Syukri Y, et al. PEGylated liposomes enhance the effect of cytotoxic drug: A review. 2023;9(3).
44. Whang YM, Yoon DH, Hwang GY, Yoon H, Park SI, Choi YW, et al. Liposome-encapsulated bacillus calmette–guérin cell wall skeleton enhances antitumor efficiency for bladder cancer in vitro and in vivo via induction of amp-activated protein kinase. 2020;12(12):3679.
45. Yoshino T, Miyazaki J, Kojima T, Kandori S, Shiga M, Kawahara T, et al. Cationized liposomal keto-mycolic acids isolated from Mycobacterium bovis bacillus Calmette-Guerin induce antitumor immunity in a syngeneic murine bladder cancer model. 2019;14(1):e0209196.
46. Zhai B, Chen P, Wang W, Liu S, Feng J, Duan T, et al. An ATF24 peptide-functionalized β-elemene-nanostructured lipid carrier combined with cisplatin for bladder cancer treatment. 2020;17(3):676.
47. Lv S, Jing R, Liu X, Shi H, Shi Y, Wang X, et al. One-step microfluidic fabrication of multi-responsive liposomes for targeted delivery of doxorubicin synergism with photothermal effect. 2021:7759-72.
48. Ghaferi M, Asadollahzadeh MJ, Akbarzadeh A, Ebrahimi Shahmabadi H, Alavi SEJIjoms. Enhanced efficacy of PEGylated liposomal cisplatin: In vitro and in vivo evaluation. 2020;21(2):559.
49. Ilyas R, Sapuan SJCOS. The preparation methods and processing of natural fibre bio-polymer composites. 2019;16(8):1068-70.
50. Wang B, Wang S, Zhang Q, Deng Y, Li X, Peng L, et al. Recent advances in polymer-based drug delivery systems for local anesthetics. 2019;96:55-67.
51. Gagliardi A, Giuliano E, Venkateswararao E, Fresta M, Bulotta S, Awasthi V, et al. Biodegradable polymeric nanoparticles for drug delivery to solid tumors. 2021;12:601626.
52. Bae Y, Kataoka KJAddr. Intelligent polymeric micelles from functional poly (ethylene glycol)-poly (amino acid) block copolymers. 2009;61(10):768-84.
53. Li G, Yuan S, Deng D, Ou T, Li Y, Sun R, et al. Fluorinated polyethylenimine to enable transmucosal delivery of photosensitizer-conjugated catalase for photodynamic therapy of orthotopic bladder tumors postintravesical instillation. 2019;29(40):1901932.
54. Poinard B, Neo SZY, Yeo ELL, Heng HPS, Neoh KG, Kah JCYJAam, et al. Polydopamine nanoparticles enhance drug release for combined photodynamic and photothermal therapy. 2018;10(25):21125-36.
55. Tan P, Cai H, Wei Q, Tang X, Zhang Q, Kopytynski M, et al. Enhanced chemo-photodynamic therapy of an enzyme-responsive prodrug in bladder cancer patient-derived xenograft models. 2021;277:121061.
56. Biswas S, Kumari P, Lakhani PM, Ghosh BJEJoPS. Recent advances in polymeric micelles for anti-cancer drug delivery. 2016;83:184-202.
57. Cagel M, Tesan FC, Bernabeu E, Salgueiro MJ, Zubillaga MB, Moretton MA, et al. Polymeric mixed micelles as nanomedicines: Achievements and perspectives. 2017;113:211-28.
58. Ghosh B, Biswas SJJoCR. Polymeric

micelles in cancer therapy: State of the art. 2021;332:127-47.

59. Zhou D, Zhang G, Gan ZJJoCR. c (RGDfK) decorated micellar drug delivery system for intravesical instilled chemotherapy of superficial bladder cancer. 2013;169(3):204-10.
60. Zhou D-H, Zhang G, Yu Q-S, Gan Z-HJCJoPS. Folic acid modified polymeric micelles for intravesical instilled chemotherapy. 2018;36:479-87.
61. Yu Q, Zhang J, Zhang G, Gan ZJMB. Synthesis and Functions of Well-defined Polymer-drug Conjugates as Efficient Nanocarriers for Intravesical Chemotherapy of Bladder Cancera. 2015;15(4):509-20.
62. Zhu G, Wang K, Qin H, Zhao X, Chen W, Xu L, et al. Internal cross-linked polymeric nanoparticles with dual sensitivity for combination therapy of muscle-invasive bladder cancer. 2020;18:1-13.
63. Xu L, Zhang Z, Wang F, Xie D, Yang S, Wang T, et al. Synthesis, characterization, and self-assembly of linear poly (ethylene oxide)-block–poly (propylene oxide)-block–poly (ε-caprolactone)(PEO–PPO–PCL) copolymers. 2013;393:174-81.
64. Lin T-Y, Li Y, Liu Q, Chen J-L, Zhang H, Lac D, et al. Novel theranostic nanoporphyrins for photodynamic diagnosis and trimodal therapy for bladder cancer. 2016;104:339-51.
65. Jin X, Zhang P, Luo L, Cheng H, Li Y, Du T, et al. Efficient intravesical therapy of bladder cancer with cationic doxorubicin nanoassemblies. 2016:4535-44.
66. Jhawat V, Gulia M, Maddiboyina B, Dutt R, Gupta SJCN. Fate and applications of superporous hydrogel systems: a review. 2020;10(4):326-41.
67. Raemdonck K, Demeester J, De Smedt SJSM. Advanced nanogel engineering for drug delivery. 2009;5(4):707-15.
68. Maddiboyina B, Desu PK, Vasam M, Challa VT, Surendra AV, Rao RS, et al. An insight of nanogels as novel drug delivery system with potential hybrid nanogel applications. 2022;33(2):262-78.
69. Maddiboyina B, Hanumanaik M, Nakkala RK, Jhawat V, Rawat P, Alam A, et al. Formulation and evaluation of gastro-retentive floating bilayer tablet for the treatment of hypertension. 2020;6(11).
70. Guo H, Xu W, Chen J, Yan L, Ding J, Hou Y, et al. Positively charged polypeptide nanogel enhances mucoadhesion and penetrability of 10-hydroxycamptothecin in orthotopic bladder carcinoma. 2017;259:136-48.
71. Babu A, Ramesh RJMd. Multifaceted applications of chitosan in cancer drug delivery and therapy. 2017;15(4):96.
72. Wang W, Meng Q, Li Q, Liu J, Zhou M, Jin Z, et al. Chitosan derivatives and their application in biomedicine. 2020;21(2):487.
73. Shanmuganathan R, Edison TNJI, LewisOscar F, Kumar P, Shanmugam S, Pugazhendhi AJIjobm. Chitosan nanopolymers: an overview of drug delivery against cancer. 2019;130:727-36.
74. Narmani A, Jafari SMJCP. Chitosan-based nanodelivery systems for cancer therapy: Recent advances. 2021;272:118464.
75. Liu Y, Wang R, Hou J, Sun B, Zhu B, Qiao Z, et al. Paclitaxel/chitosan nanosupensions provide enhanced intravesical bladder cancer therapy with sustained and prolonged delivery of paclitaxel. 2018;1(6):1992-2001.

76. Ay Şenyiğit Z, Karavana SY, İlem-Özdemir D, Çalışkan Ç, Waldner C, Şen S, et al. Design and evaluation of an intravesical delivery system for superficial bladder cancer: preparation of gemcitabine HCl-loaded chitosan–thioglycolic acid nanoparticles and comparison of chitosan/poloxamer gels as carriers. 2015:6493-507.

77. Wang Y, Qian J, Yang M, Xu W, Wang J, Hou G, et al. Doxorubicin/cisplatin co-loaded hyaluronic acid/chitosan-based nanoparticles for in vitro synergistic combination chemotherapy of breast cancer. 2019;225:115206.

78. Ghoshal A, Goswami U, Sahoo AK, Chattopadhyay A, Ghosh SSJABS, Engineering. Targeting Wnt canonical signaling by recombinant sFRP1 bound luminescent Au-nanocluster embedded nanoparticles in cancer theranostics. 2015;1(12):1256-66.

79. Burjak M, Bogataj M, Velnar M, Grabnar I, Mrhar AJIjop. The study of drug release from microspheres adhered on pig vesical mucosa. 2001;224(1-2):123-30.

80. Jiao B, Liu K, Gong H, Ding Z, Xu X, Ren J, et al. Bladder cancer selective chemotherapy with potent NQO1 substrate co-loaded prodrug nanoparticles. 2022;347:632-48.

81. Sun R, Liu X, Li G, Wang H, Luo Y, Huang G, et al. Photoactivated H2 nanogenerator for enhanced chemotherapy of bladder cancer. 2020;14(7):8135-48.

82. Martin DT, Steinbach JM, Liu J, Shimizu S, Kaimakliotis HZ, Wheeler MA, et al. Surface-modified nanoparticles enhance transurothelial penetration and delivery of survivin siRNA in treating bladder cancer. 2014;13(1):71-81.

83. Liang Y, Wang Y, Wang L, Liang Z, Li D, Xu X, et al. Self-crosslinkable chitosan-hyaluronic acid dialdehyde nanoparticles for CD44-targeted siRNA delivery to treat bladder cancer. 2021;6(2):433-46.

84. Erdoğar N, Iskit AB, Eroğlu H, Sargon MF, Mungan N, Bilensoy EJJoN, et al. Antitumor efficacy of bacillus calmette-guerin loaded cationic nanoparticles for intravesical immunotherapy of bladder tumor induced rat model. 2015;15(12):10156-64.

85. Erdoğar N, Iskit AB, Mungan NA, Bilensoy EJJom. Prolonged retention and in vivo evaluation of cationic nanoparticles loaded with Mitomycin C designed for intravesical chemotherapy of bladder tumours. 2012;29(6):576-82.

86. Lu S, Xu L, Kang ET, Mahendran R, Chiong E, Neoh KGJEJoPS. Co-delivery of peptide-modified cisplatin and doxorubicin via mucoadhesive nanocapsules for potential synergistic intravesical chemotherapy of non-muscle-invasive bladder cancer. 2016;84:103-15.

87. Kogan A, Garti NJAic, science i. Microemulsions as transdermal drug delivery vehicles. 2006;123:369-85.

88. Neubi GMN, Opoku-Damoah Y, Gu X, Han Y, Zhou J, Ding YJBs. Bio-inspired drug delivery systems: an emerging platform for targeted cancer therapy. 2018;6(5):958-73.

89. Verma P, Meher JG, Asthana S, Pawar VK, Chaurasia M, Chourasia MKJDd. Perspectives of nanoemulsion assisted oral delivery of docetaxel for improved chemotherapy of cancer. 2016;23(2):479-88.

90. Hörmann K, Zimmer AJJocr. Drug delivery and drug targeting with parenteral lipid nanoemulsions—A review. 2016;223:85-98.

91. Wilhelm S, Tavares AJ, Dai Q, Ohta S, Audet J, Dvorak HF, et al. Analysis of nanoparticle delivery to tumours. 2016;1(5):1-12.

92. Chen T-Y, Tsai M-J, Chang L-C, Wu P-CJP. Co-delivery of cisplatin and gemcitabine via viscous nanoemulsion for potential synergistic intravesical chemotherapy. 2020;12(10):949.

93. Wu MX, Yang YWJAM. Metal–organic framework (MOF)-based drug/cargo delivery and cancer therapy. 2017;29(23):1606134.

94. Gao P, Chen Y, Pan W, Li N, Liu Z, Tang BJAC. Antitumor agents based on metal–organic frameworks. 2021;133(31):16901-14.

95. Chen Y, Gu L, Ma B, Li X, Mei Y, Zhou J, et al. Photoactivatable metal organic framework for synergistic ferroptosis and photodynamic therapy using 450 nm laser. 2023;454:140438.

96. Zhu H, Wang Y, Wei T, Zhao X, Li F, Li Y, et al. KAT8/MOF-mediated anti-cancer mechanism of gemcitabine in human bladder cancer cells. 2021;29(2):184.

97. Li F, Xu M, Zhuang JJB, Bioelectronics. Dual biomineralized metal− organic frameworks-mediated conversion of chemical energy to electricity enabling portable PEC sensing of telomerase activity in bladder cancer tissues. 2022;204:114070.

98. Tiwari PM, Vig K, Dennis VA, Singh SRJN. Functionalized gold nanoparticles and their biomedical applications. 2011;1(1):31-63.

99. Singh P, Pandit S, Mokkapati V, Garg A, Ravikumar V, Mijakovic IJIjoms. Gold nanoparticles in diagnostics and therapeutics for human cancer. 2018;19(7):1979.

100. Zhou W, Gao X, Liu D, Chen XJCr. Gold nanoparticles for in vitro diagnostics. 2015;115(19):10575-636.

101. Amendola V, Pilot R, Frasconi M, Maragò OM, Iatì MAJJopCm. Surface plasmon resonance in gold nanoparticles: a review. 2017;29(20):203002.

102. Daei S, Ziamajidi N, Abbasalipourkabir R, Khanaki K, Bahreini FJBTER. Anticancer effects of gold nanoparticles by inducing apoptosis in bladder cancer 5637 cells. 2022;200(6):2673-83.

103. Li Z, Ren D, Chen C, Sun L, Fang KJCBI. OSU-T315 and doxorubicin synergistically induce apoptosis via mitochondrial pathway in bladder cancer cells. 2022;46(10):1672-81.

104. Hsu C-W, Cheng N-C, Liao M-Y, Cheng T-Y, Chiu Y-CJN. Development of folic acid-conjugated and methylene blue-adsorbed Au@ TNA nanoparticles for enhanced photodynamic therapy of bladder cancer cells. 2020;10(7):1351.

105. Liao M-Y, Huang T-C, Chin Y-C, Cheng T-Y, Lin G-MJAABM. Surfactant-free green synthesis of Au@ chlorophyll nanorods for NIR PDT-elicited CDT in bladder cancer therapy. 2022;5(6):2819-33.

106. Safarik I, Safarikova M. Magnetic Nanoparticles for In Vitro Biological and Medical Applications: CRC Press: Boca Ration, USA; 2012.

107. Liu K, Mo Q, Ding Z, Lai S, Ren J, Yu QJEoDS. Nano theranostics involved in bladder cancer treatment. 2023;1(2):81-106.

108. Gupta AK, Gupta MJb. Synthesis and surface engineering of iron oxide nanoparticles for biomedical applications.

2005;26(18):3995-4021.

109. Yallapu MM, Othman SF, Curtis ET, Gupta BK, Jaggi M, Chauhan SCJB. Multi-functional magnetic nanoparticles for magnetic resonance imaging and cancer therapy. 2011;32(7):1890-905.

110. Khanna L, Verma N, Tripathi SJJoA, Compounds. Burgeoning tool of biomedical applications-Superparamagnetic nanoparticles. 2018;752:332-53.

111. Farzin A, Etesami SA, Quint J, Memic A, Tamayol AJAhm. Magnetic nanoparticles in cancer therapy and diagnosis. 2020;9(9):1901058.

112. Tao K, Liu S, Wang L, Qiu H, Li B, Zhang M, et al. Targeted multifunctional nanomaterials with MRI, chemotherapy and photothermal therapy for the diagnosis and treatment of bladder cancer. 2020;8(1):342-52.

113. Sun X, Song X, Guo P, Zhang D, Zuo S, Leng K, et al. Improvement of the bladder perfusion curative effect through tight junction protein degradation induced by magnetic temperature-sensitive hydrogels. 2022;10:958072.

114. Qi A, Wang C, Ni S, Meng Y, Wang T, Yue Z, et al. Intravesical mucoadhesive hydrogel induces chemoresistant bladder cancer ferroptosis through delivering iron oxide nanoparticles in a three-tier strategy. 2021;13(44):52374-84.

115. Suo N, Wang M, Jin Y, Ding J, Gao X, Sun X, et al. Magnetic multiwalled carbon nanotubes with controlled release of epirubicin: an intravesical instillation system for bladder cancer. 2019:1241-54.

116. Huang C, Neoh KG, Xu L, Kang ET, Chiong EJB. Polymeric nanoparticles with encapsulated superparamagnetic iron oxide and conjugated cisplatin for potential bladder cancer therapy. 2012;13(8):2513-20.

117. Wang Y-P, Liao Y-T, Liu C-H, Yu J, Alamri HR, Alothman ZA, et al. Trifunctional Fe3O4/CaP/Alginate core–shell–corona nanoparticles for magnetically guided, pH-responsive, and chemically targeted chemotherapy. 2017;3(10):2366-74.

118. Chin Y-C, Yang L-X, Hsu F-T, Hsu C-W, Chang T-W, Chen H-Y, et al. Iron oxide@ chlorophyll clustered nanoparticles eliminate bladder cancer by photodynamic immunotherapy-initiated ferroptosis and immunostimulation. 2022;20(1):373.

119. Lin W, Liu H, Chen L, Chen J, Zhang D, Cheng Q, et al. Pre-clinical MRI-guided intravesical instillation theranosis of bladder cancer by tumor-selective oxygen nanogenerator. 2021;38:101124.

120. Castillo RR, Lozano D, Vallet-Regí MJP. Mesoporous silica nanoparticles as carriers for therapeutic biomolecules. 2020;12(5):432.

121. Jafari S, Derakhshankhah H, Alaei L, Fattahi A, Varnamkhasti BS, Saboury AAJB, et al. Mesoporous silica nanoparticles for therapeutic/diagnostic applications. 2019;109:1100-11.

122. Porrang S, Davaran S, Rahemi N, Allahyari S, Mostafavi EJIJoN. How advancing are mesoporous silica nanoparticles? A comprehensive review of the literature. 2022:1803-27.

123. Zhang Q, Neoh KG, Xu L, Lu S, Kang ET, Mahendran R, et al. Functionalized mesoporous silica nanoparticles with mucoadhesive and sustained drug release properties for potential bladder cancer therapy. 2014;30(21):6151-61.

124. Wei Y, Gao L, Wang L, Shi L, Wei E, Zhou B, et al. Polydopamine and peptide decorated doxorubicin-loaded mesoporous silica nanoparticles as a targeted drug delivery system for bladder cancer therapy. 2017;24(1):681-91.

125. Wang B, Zhang K, Wang J, Zhao R, Zhang Q, Kong XJC, et al. Poly (amidoamine)-modified mesoporous silica nanoparticles as a mucoadhesive drug delivery system for potential bladder cancer therapy. 2020;189:110832.

126. Hortelao AC, Carrascosa R, Murillo-Cremaes N, Patino T, Sanchez SJAN. Targeting 3D bladder cancer spheroids with urease-powered nanomotors. 2018;13(1):429-39.

127. Haddick L, Zhang W, Reinhard S, Möller K, Engelke H, Wagner E, et al. Particle-size-dependent delivery of antitumoral miRNA using targeted mesoporous silica nanoparticles. 2020;12(6):505.

128. Shahidi M, Abazari O, Dayati P, Bakhshi A, Zavarreza J, Modarresi MH, et al. Multicomponent siRNA/miRNA-loaded modified mesoporous silica nanoparticles targeted bladder cancer for a highly effective combination therapy. 2022;10:949704.

129. Borzęcka W, Pereira PM, Fernandes R, Trindade T, Torres T, Tome JPJJoMCB. Spherical and rod shaped mesoporous silica nanoparticles for cancer-targeted and photosensitizer delivery in photodynamic therapy. 2022;10(17):3248-59.

130. Sweeney SK, Luo Y, O'Donnell MA, Assouline JGJJobn. Peptide-mediated targeting mesoporous silica nanoparticles: a novel tool for fighting bladder cancer. 2017;13(2):232-42.

131. Sukhanova A, Bozrova S, Sokolov P, Berestovoy M, Karaulov A, Nabiev IJNrl. Dependence of nanoparticle toxicity on their physical and chemical properties. 2018;13:1-21.

132. Rajendiran K, Zhao Z, Pei D-S, Fu AJP. Antimicrobial activity and mechanism of functionalized quantum dots. 2019;11(10):1670.

133. Yuan R, Rao T, Cheng F, Yu W-M, Ruan Y, Zhang X-B, et al. Quantum dot-based fluorescent probes for targeted imaging of the EJ human bladder urothelial cancer cell line. 2018;16(6):4779-83.

134. Pan Y, Chang T, Marcq G, Liu C, Kiss B, Rouse R, et al. In vivo biodistribution and toxicity of intravesical administration of quantum dots for optical molecular imaging of bladder cancer. 2017;7(1):9309.

135. Manan FAA, Yusof NA, Abdullah J, Mohammad F, Nurdin A, Yazan LS, et al. Drug release profiles of mitomycin c encapsulated quantum dots–chitosan nanocarrier system for the possible treatment of non-muscle invasive bladder cancer. 2021;13(9):1379.

136. Isaac KM, Sabaraya IV, Ghousifam N, Das D, Pekkanen AM, Romanovicz DK, et al. Functionalization of single-walled carbon nanohorns for simultaneous fluorescence imaging and cisplatin delivery in vitro. 2018;138:309-18.

137. He Q, Zhang Z, Gao F, Li Y, Shi JJs. In vivo biodistribution and urinary excretion of mesoporous silica nanoparticles: effects of particle size and PEGylation. 2011;7(2):271-80.

138. Fu C, Liu T, Li L, Liu H, Chen D, Tang FJB. The absorption, distribution, excretion and toxicity of mesoporous silica

nanoparticles in mice following different exposure routes. 2013;34(10):2565-75.

139. Blanco E, Shen H, Ferrari MJNb. Principles of nanoparticle design for overcoming biological barriers to drug delivery. 2015;33(9):941-51.

140. Su C, Liu Y, Li R, Wu W, Fawcett JP, Gu JJAddr. Absorption, distribution, metabolism and excretion of the biomaterials used in Nanocarrier drug delivery systems. 2019;143:97-114.

141. Ekdawi SN, Stewart JM, Dunne M, Stapleton S, Mitsakakis N, Dou YN, et al. Spatial and temporal mapping of heterogeneity in liposome uptake and microvascular distribution in an orthotopic tumor xenograft model. 2015;207:101-11.

142. Liang X, Wang H, Grice JE, Li L, Liu X, Xu ZP, et al. Physiologically based pharmacokinetic model for long-circulating inorganic nanoparticles. 2016;16(2):939-45.

143. Zhang Y-N, Poon W, Tavares AJ, McGilvray ID, Chan WCJJocr. Nanoparticle–liver interactions: Cellular uptake and hepatobiliary elimination. 2016;240:332-48.

144. Yuan D, He H, Wu Y, Fan J, Cao YJJops. Physiologically based pharmacokinetic modeling of nanoparticles. 2019;108(1):58-72.

145. Zhou C, Long M, Qin Y, Sun X, Zheng JJAC. Luminescent gold nanoparticles with efficient renal clearance. 2011;50(14):3168.

146. Huang X, Li L, Liu T, Hao N, Liu H, Chen D, et al. The shape effect of mesoporous silica nanoparticles on biodistribution, clearance, and biocompatibility in vivo. 2011;5(7):5390-9.

147. Greish K, Thiagarajan G, Herd H, Price R, Bauer H, Hubbard D, et al. Size and surface charge significantly influence the toxicity of silica and dendritic nanoparticles. 2012;6(7):713-23.

148. Pisani C, Rascol E, Dorandeu C, Charnay C, Guari Y, Chopineau J, et al. Biocompatibility assessment of functionalized magnetic mesoporous silica nanoparticles in human HepaRG cells. 2017;11(7):871-90.

149. Lopez-Chaves C, Soto-Alvaredo J, Montes-Bayon M, Bettmer J, Llopis J, Sanchez-Gonzalez CJNN, Biology, et al. Gold nanoparticles: distribution, bioaccumulation and toxicity. In vitro and in vivo studies. 2018;14(1):1-12.

150. Xie X, Liao J, Shao X, Li Q, Lin YJSr. The effect of shape on cellular uptake of gold nanoparticles in the forms of stars, rods, and triangles. 2017;7(1):3827.

151. Kurkov SV, Loftsson TJIjop. Cyclodextrins. 2013;453(1):167-80.

152. Liu B, Gao X, Han B, Chen G, Song S, Bo HJJon, et al. Mouse model to explore the therapeutic effect of nano-doxorubicin drug delivery system on bladder cancer. 2021;21(2):914-20.

153. Mikhail AS, Negussie AH, Pritchard WF, Haemmerich D, Woods D, Bakhutashvili I, et al. Lyso-thermosensitive liposomal doxorubicin for treatment of bladder cancer. 2017;33(7):733-40.

154. Pan A, Zhang H, Li Y, Lin T-y, Wang F, Lee J, et al. Disulfide-crosslinked nanomicelles confer cancer-specific drug delivery and improve efficacy of paclitaxel in bladder cancer. 2016;27(42):425103.

155. Zheng B, Liu Z, Wang H, Sun L, Lai W-F, Zhang H, et al. R11 modified tumor cell membrane nanovesicle-camouflaged

nanoparticles with enhanced targeting and mucus-penetrating efficiency for intravesical chemotherapy for bladder cancer. 2022;351:834-46.

156. Xiong Q, Liu A, Ren Q, Xue Y, Yu X, Ying Y, et al. Cuprous oxide nanoparticles trigger reactive oxygen species-induced apoptosis through activation of erk-dependent autophagy in bladder cancer. 2020;11(5):366.

157. Guo H, Li F, Qiu H, Xu W, Li P, Hou Y, et al. Synergistically enhanced mucoadhesive and penetrable polypeptide nanogel for efficient drug delivery to orthotopic bladder cancer. 2020.

158. Qi L, Liu C, Zhang Y, Zhang Z, Duan H, Zhao H, et al. Development of mitomycin C-loaded nanoparticles prepared using the micellar assembly driven by the combined effect of hydrogen bonding and π–π stacking and its therapeutic application in bladder cancer. 2021;13(11):1776.

159. Xu X, Liu K, Jiao B, Luo K, Ren J, Zhang G, et al. Mucoadhesive nanoparticles based on ROS activated gambogic acid prodrug for safe and efficient intravesical instillation chemotherapy of bladder cancer. 2020;324:493-504.

160. Ambrosio L, Argenziano M, Cucci MA, Grattarola M, De Graaf IA, Dianzani C, et al. Carbosilane dendrimers loaded with siRNA targeting Nrf2 as a tool to overcome cisplatin chemoresistance in bladder cancer cells. 2020;9(10):993.

161. Arista-Romero M, Cascante A, Fornaguera C, Borrós SJP. Role of survivin in bladder cancer: Issues to be overcome when designing an efficient dual nano-therapy. 2021;13(11):1959.

162. Yu C, Zhang Y, Wang N, Wei W, Cao K, Zhang Q, et al. Treatment of bladder cancer by geoinspired synthetic chrysotile nanocarrier-delivered circPRMT5 siRNA. 2022;26(1):6.

163. Liu J, Zhang Y, Zeng H, Wang L, Zhang Q, Wu P, et al. Fe-doped chrysotile nanotubes containing siRNAs to silence SPAG5 to treat bladder cancer. 2021;19(1):189.

164. Zhou Q, Ding W, Qian Z, Zhu Q, Sun C, Yu Q, et al. Immunotherapy strategy targeting programmed cell death ligand 1 and CD73 with macrophage-derived mimetic nanovesicles to treat bladder cancer. 2021;18(11):4015-28.

165. Wu X, Wei Y, Lin R, Chen P, Hong Z, Zeng R, et al. Multi-responsive mesoporous polydopamine composite nanorods cooperate with nano-enzyme and photosensitiser for intensive immunotherapy of bladder cancer. 2022;167(2):247-62.

166. Reis I, Tibo L, Socca E, De Souza B, Durán N, Fávaro WJT, et al. OncoTherad®(MRB-CFI-1) nano-immunotherapy reduced tumoral progression in non-muscle invasive bladder cancer through activation of Toll-like signaling pathway. 2022;76:101762.

167. Samaddar S, Mazur J, Sargent J, Thompson DHJAabm. Immunostimulatory response of RWFV peptide-targeted lipid nanoparticles on bladder tumor associated cells. 2021;4(4):3178-88.

168. Terán-Navarro H, Zeoli A, Salines-Cuevas D, Marradi M, Montoya N, Gonzalez-Lopez E, et al. Gold glyconanoparticles combined with 91–99 peptide of the bacterial toxin, listeriolysin O, are efficient immunotherapies in experimental bladder tumors.

2022;14(10):2413.

169. Chen W-H, Yu K-J, Jhou J-W, Pang H-H, Weng W-H, Lin W-S, et al. Glucose/glutathione co-triggered tumor hypoxia relief and Chemodynamic therapy to enhance Photothermal therapy in bladder cancer. 2021;4(10):7485-96.

170. Shang W, Peng L, Guo P, Hui H, Yang X, Tian JJABS, et al. Metal–organic frameworks as a theranostic nanoplatform for combinatorial chemophotothermal therapy adapted to different administration. 2019;6(2):1008-16.

171. Gao H, Bi Y, Wang X, Wang M, Zhou M, Lu H, et al. Near-infrared guided thermal-responsive nanomedicine against orthotopic superficial bladder cancer. 2017;3(12):3628-34.