Applications of Nanotechnology in Bladder Cancer Therapy

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ABSTRACT
Effective therapies can prevent superficial bladder cancer from developing into muscle-invasive stage or more severe stages which require radical cystectomy and negatively affect life quality. In terms of therapeutic approaches against superficial bladder cancer, intravesical (regional) therapy has several advantages over oral (systemic) therapy. Though urologists can directly deliver drugs to bladder lesions by intravesical instillation after transurethral resection, the efficacy of conventional drug delivery is usually low due to the bladder permeability barrier and bladder periodical discharge. Nanoparticles have been well developed as pharmaceutical carriers. By their versatile properties, nanoparticles can greatly improve the interactions between urothelium and drugs and also enhance the penetration of drugs into urothelium with lesions, which dramatically improves therapeutic efficacy. In this review, we discuss the advances of nanotechnology in bladder cancer therapy by different types of nanoparticles with different encapsulating materials.

Keywords: bladder cancer, nanoparticle, liposome, intravesical

1. INTRODUCTION
Bladder cancer is the fourth most common cancer in American men, and is estimated to be diagnosed in 73,510 people and to cause 14,880 deaths in the US in 2012 [1]. Bladder cancer is also the cancer which has the highest cost from diagnosis to death per person and is the fifth most expensive cancer to treat overall [2]. However, the cost of treatments associated with bladder cancer is not proportionate to the incidence of bladder cancer, which implies that the efficacy of follow-up therapies needs to be greatly improved. About 70% of bladder cancer patients are initially diagnosed as in superficial stage [3], and receive transurethral resection (TUR) to remove superficial tumors followed by intravesical chemotherapeutics, such as mitomycin C, Adriamycin, and bacille Calmette-Guérin (BCG) to eradicate residual cancer cells. However, 50–70% of superficial lesions recur and about 10–30 % develop into muscle-invasive tumors [3–5]. The standard
treatment for muscle-invasive bladder cancer is radical cystectomy which can cause loss of urinary or sexual functions [6]. Therefore, effective therapeutic approaches against superficial bladder cancer are greatly needed to ensure patients’ quality of life.

Since most bladder cancers are superficial, a cancerous bladder is an ideal organ for regional therapy. High grade superficial tumors are visible by cystoscopy and can be removed by electrocautery without invasive surgery. Drugs can be delivered to the bladder lesions through intravesical instillation without specific homing concerns. Moreover, the contact of drugs with bladder lesions does not go through the circulatory system, hence higher dosage of drugs can be loaded without inducing severe systemic side effects to other organs. The luminal side of the urothelium develops numerous rigid-looking plaques which cover the urothelial surface. The outer leaflet of these plaques is twice as thick as the inner leaflet. Therefore, this layer of specialized plaques is termed the asymmetric unit membrane. The specialized asymmetric unit membrane on top of the urothelium forms a barrier and only allows less than 5% of the drug dose to be absorbed into the circulation system [7–9], thus ensuring the dominance of intravesical treatment in bladder cancer therapy.

Nanoparticles have been well developed and applied as pharmaceutical carriers in cancer therapies due to their versatile capabilities, such as carrying various drugs, protecting drug from degradation, promoting interaction between drugs and target cells, or enhancing permeability of drugs [10–12]. These advantages can address the weaknesses of conventional intravesical drug delivery. Scientists have developed variant types of nanoparticles as drug carriers for intravesical therapy and have achieved positive results in preclinical studies. In this review, we first introduce the structure of the bladder urothelium and bladder permeability barrier. The second part introduces the bladder diseases, including bladder cancers and painful bladder syndrome (PBS). The third part summarizes the applications of different nanoparticles in intravesical therapy. Finally, perspectives for nanotechnology in bladder cancer therapy are discussed.

2. BLADDER STRUCTURE AND BARRIER

2.1. Bladder Structure

The bladder is a hollow organ which stores urine secreted from the kidneys. The lumen capacity of bladder is about 400–600 mL. When the urine amount reaches about 150–300 mL, an urge to urinate is induced [13]. The bladder wall is elastic and impermeable, allowing the bladder to store urine for a short term while preventing urine and contained waste substances from penetrating through the bladder wall. The bladder wall is composed of multiple layers of tissue. The layers from outside to inside are: adventitia, detrusor muscle, submucosa, and mucosa which consists of lamina propria and transitional epithelium (urothelium). The urothelium is the first lining layer within the bladder lumen and serves as a bladder permeability barrier [14]. The urothelium is composed of three different cells: basal cells, intermediate cells, and umbrella cells (listed from outside to inside) [15]. These three cell types differ in their distinct morphologies [16]. Basal cells have diameters of 5–10 µm and fuse to form intermediate cells with a diameter of 20 µm. The intermediate cells further fuse to form umbrella cells with diameters of 50–120 µm, depending on the degree of bladder stretch [17].
2.2. Bladder Permeability Barrier
Umbrella cells have two remarkable morphological features that differ from basal and intermediate cells [15]. First, they have scalloped-shape plaques covering the apical membrane, which makes the outer leaflet of the apical membrane thicker than the inner leaflet and forms the asymmetric unit membrane [18]. Second, umbrella cells have many cytoplasmic vesicles which are associated with cytoskeletal fibrils [19]. Each plaque above the umbrella cell membrane has about 1000 subunits and are composed of four uroplakins, UPIa (27 kDa), UPIb (28 kDa), UPII (15 kDa), and UPIII (47 kDa) [20]. Each subunit is arranged hexagonally with an inner loop composed of six large particles (UPIa or UPIb) and an outer loop composed of six small particles (UPII or UPIII) [13, 15, 21]. The barrier function of umbrella cells is established by the tight arrangement of these scalloped-shape plaques and further enhanced by a mucin layer on the luminal side. This mucin layer is composed of glycosaminoglycans (GAGs), which are hydrophilic and form an aqueous layer upon umbrella cells. Therefore, this GAG layer can prevent urine substances from adhering to the bladder lumen [22].

3. BLADDER CANCER AND DISEASE
3.1. Bladder Cancer
Over 90% of bladder cancers (BCa) are derived from bladder urothelial cells; i.e., urothelial carcinoma. Other BCa types are squamous cell carcinoma (originated from squamous cells as a result of chronic bladder inflammation) and adenocarcinoma (originated from the cells which make up glands).

Many factors are associated with bladder cancer incidence. First, smoking is the most potent factor to cause bladder cancer [23, 24]. Certain chemicals in cigarettes have been identified to be associated with bladder cancer [25]. Second, exposures to some carcinogens in the work place, such as benzidine or aromatic amines, also contribute to bladder cancer. Occupations at high risk of bladder cancer are bus drivers, rubber workers, motor mechanics, leather workers, blacksmiths, machine setters and mechanics [26]. Third, salted and barbecued meats may also be associated with bladder tumorigenesis, since those foods contain carcinogens such as N-nitroso compounds and heterocyclic amines [27].

The diagnosis of bladder cancer is determined by a positive cytology, cystoscopy and biopsy. Common symptoms of bladder cancer include painless gross hematuria (the presence of red blood cells in the urine), urinary frequency, bladder irritability, urgency, and dysuria. Bladder cancer staging is classified by the location and spread of tumors (Figure 1).

According to the American Joint Committee on Cancer (AJCC) TNM staging system, tumor staging is described as below. TX: Main tumor cannot be assessed due to lack of information. T0: No evidence of a primary tumor. Ta: Non-invasive papillary carcinoma. Tis: Non-invasive flat carcinoma. T1: The tumor has grown from the urothelial layer into the connective tissue below. T2: The tumor has grown into the muscle layer. T3: The tumor has grown through the muscle layer and into the fatty tissue. T4: The tumor has spread beyond the fatty tissue and into adjacent organs or tissues. Among all stages of bladder cancer, only non-muscle invasive cancers (Ta, Tis, and T1) are suitable for intravesical therapy.
3.2. Painful Bladder Syndrome (PBS)

Painful bladder syndrome (PBS), also known as interstitial cystitis, is a condition of chronic bladder pain with syndromes of irritation, nocturia, urgency, and frequency [28–31], while other abnormal bladder conditions have been excluded. PBS is a debilitating and chronic disease which causes negative impact on life quality of patients [32]. PBS can result from various urological abnormalities, such as endometriosis or bladder cancer [33–38]. Since the etiology of PBS remains incompletely understood, all of the proposed therapeutic approaches are based on empirical evidence [32]. Factors that contribute to PBS include infection, allergic reaction, autoimmune response, neurogenic inflammation, urothelial dysfunction, and genetic factors [39, 40]. Many studies have indicated that the symptoms of PBS are derived from inflammation in the bladder [41]. Animal studies of PBS further showed that the accumulation of neutrophils in the bladder wall induces a high level of inflammatory cytokines and further activates some inflammatory gene expression [42, 43].

**Figure 1.** The staging of bladder cancer and therapeutic treatments. The staging of bladder cancer is based on the location and spread of bladder cancer cells. Ta: Non-invasive papillary carcinoma; T1: The tumor has grown from urothelial layer into connective tissue (stroma); T2: The tumor has grown into the muscle layer; T3: The tumor has grown through the muscle layer and into the fatty tissue; T4: The tumor has spread beyond the fatty tissue and into adjacent organs or tissues. For Ta or T1 stage of bladder cancer, patients receive transurethral resection to remove superficial tumors followed by intravesical therapeutics. For T2, T3, and T4 stages of bladder cancer, radical cystectomy is the standard treatment for the patients.
4. LIPOSOMES AND NANOPARTICLES IN INTRAVESICAL THERAPY

4.1. Liposomes

Liposomes are artificially-synthesized phospholipid vesicles with bilayer membrane structure, which were first developed by Alec Bangham in 1961 [44]. Not just limited to biophysical research, liposomes have been developed and applied in carrying different molecules such as drug molecules, nucleotides, protein, and plasmids. The binding of liposomes to human bladder urothelial cancer cell lines potentiates the application of liposomes in bladder cancer therapy [13]. Johnson et al. [45] found that negatively charged large multilamellar vesicles (MLVs) show improved binding to four different human bladder tumor cell lines (253J, J82, T24, TCCSUP) compared to small sonicated vesicles or vesicles consisting of uncharged phosphatidylcholine (PC). Furthermore, MLV specifically bind to tumor cells but not to normal fetal bladder cells. These data suggest that liposomes may be ideal pharmaceutical carriers for intravesical therapy against bladder cancer.

Overexpression of oncogenes in the urothelium is one of the major causes of urothelial carcinoma induction [46]. Therefore, silencing of the activated oncogenes via small interfering RNA (siRNA) can be an effective approach to suppress cancer growth. Polo-like kinase-1 (PLK-1) is one of the regulators of mitotic progression in mammalian cells [47], which has been associated with the development of variant cancers [48–51]. Nogawa et al. [52] first reported that PLK-1 is associated with grades of bladder cancer and the survival rate of bladder cancer patients. By intravesically instilling a complex of PLK-1 siRNA and liposomes into the mouse bladder with an orthotopic tumor, Nogawa et al. successfully transfected PLK-1 siRNA into cancer cells and reduced PLK-1 expression, resulting in suppression of cancer growth in this mouse model. However, the effect of liposomes alone was not investigated [52]. This was the first study showing the suppression of bladder cancer growth by intravesical delivery of siRNA/liposomes in a mouse model. Seth et al. [53] further used PLK-1 siRNA/liposomes to suppress orthotopic bladder cancer growth in a mouse model. Besides the successes in mouse models, Arum et al. [54] showed that intravesical delivery of siRNA/liposomes can successfully transfect siRNA into urothelium in a rat model.

Intravesical administration of anti-proliferative agents is one of the current therapeutic approaches against bladder cancer. Liposomes encapsulated with cytotoxic agents have been shown to improve the efficacy of intravesical therapy. Killion et al. [55] first demonstrated that recombinant human interferon alpha (IFN-α) encapsulated in liposomes achieves significantly greater cell growth inhibition on bladder cancer cell line 253J than free IFN-α alone or liposomes with saline. Interestingly, the same study also found that a subline of 253J, originally resistant to free IFN-α, became sensitive to IFN-α encapsulated in liposomes. Frangos et al. [56] further demonstrated that intravesical administration of radiolabeled IFN-α or radiolabeled liposomes did not spread to distant organs.

The encapsulation of small peptides in liposomes is an alternative approach against bladder cancer. Dinney et al. [57] showed that intravesical administration of encapsulated synthetic lipophilic muramyl tripeptide phosphatidylethanolamine (MTP-PE) can effectively eradicate orthotopically implanted human transitional cell carcinoma cells (253J-V) in athymic nude mice. After treatment of liposome/MTP-PE,
activated macrophages were found in the bladders of mice but not in the bladders of control mice not treated with liposome/MTP-PE. In the same study, *in vitro* data showed liposome/MTP-PE increased the cytotoxicity of macrophages against 253J-V cells.

Intravesical administration of plasmid-containing liposomes is also feasible in bladder cancer therapy. Many studies have demonstrated that transfection of some cytokine genes, such as IL-2 [58, 59], IL-4 [60], IL-12 [61], interferon-gamma [62], and granulocyte-macrophage colony-stimulating factor [63], into tumor cells can induce antitumor immune responses and cause growth suppression of pre-established tumors in animals. Horiguchi *et al.* [64] demonstrated that intravesical instillation of plasmid (IL-2) encapsulated in cationic liposomes can sufficiently transflect IL-2 gene into orthotopically established murine bladder tumors and further eradicate tumors and increase animal survival rate compared to control. This study of *in situ* intravesical IL-2-liposome delivery was one of the first to suggest this direction of immunotherapy against bladder cancer.

Conjugation of specific proteins to liposomes can promote the tumor-selective accumulation of liposomes. Transferrin receptor is overexpressed in bladder transitional cell carcinoma and little expressed in normal urothelium [65]. Derycke *et al.* [66] showed that conjugation of transferrin to liposomes can deliver encapsulated photosensitizer mainly into bladder tumoral tissue and little into normal urothelium and stromal tissue, suggesting that transferrin-conjugated liposome could be a promising tool for tumoral selective therapy for superficial bladder cancer.

Besides serving as pharmaceutical carriers, liposomes alone can directly contribute to bladder disease therapy. PBS has been associated with dysfunction or leaky urothelium. Therefore, improving the urothelial barrier function could be one therapeutic goal. Fraser *et al.* [67] demonstrated that intravesical instillation of liposomes could enhance barrier function of a chemical-induced dysfunctional urothelium and also increase resistance to irritant penetration in a rat model. Tyagi *et al.* [68] further showed that intravesical administration of empty liposomes of uncharged zwitterionic phospholipids, but not cationic or anionic phospholipids, can reduce protamine sulphate (PS) induced irritation and also decrease PS induced bladder contraction frequency in a rat model. Moreover, intravesical liposomes with botulinum toxin and tacrolimus have been investigated in a preclinical study on overactive bladder, and inflammatory cystitis [69, 70]. In a clinical study, Chuang *et al.* [71] demonstrated that intravesical liposomes show similar therapeutic efficacy as oral pentosan polysulfate sodium, which is approved by the U.S. Food & Drug Administration for the treatment of PBS. Lee *et al.* [72] also indicated that intravesical liposomes can improve the pain score of patients with PBS and do not cause any unanticipated adverse effect.

### 4.2. Protein Nanoparticles

Protein nanoparticles are composed of biological components and hence have biocompatible, biodegradable, non-antigenic properties, and are easily amenable to particle surface modification and covalent attachment of drugs [13, 73]. While protein nanoparticles have been employed as pharmaceutical carriers in multiple cancer therapies [74, 75], blood protein albumin has attracted most of the attention as a pharmaceutical carrier and has also been well characterized in bladder cancer studies.
Mckiernan et al. [76] demonstrated that intravesical nanoparticle albumin-bound paclitaxel (Abraxane®, ABI-007) has higher solubility and lower toxicity than docetaxel in systemic therapy, and can achieve the maximum deliverable dose while limiting cytotoxicity in clinical applications. In the intravesical therapy, commercial paclitaxel contains Cremophor which causes some micelle formation and interferes with paclitaxel’s transportation across the urothelium. To improve the delivery efficiency of paclitaxel in intravesical therapy against bladder cancer, Lu et al. [77] developed a paclitaxel-loaded gelatin protein nanoparticle for intravesical therapy. Using a canine model, they showed that an intravesical dose of paclitaxel-loaded protein nanoparticles can release 2.6-fold higher drug concentration than Cremophor-formulated paclitaxel in the urothelium and lamina propria tissue layers. Therefore, gelatin-based protein nanoparticles can provide a more extensive delivery for intravesical therapy. For the application of protein nanoparticles in clinical study, in a phase I clinical trial, nanoparticle albumin-bound paclitaxel was applied in intravesical therapy for BCG refractory non-muscle invasive bladder cancer [76], and exhibited minimal toxicity and systemic absorption in patients.

4.3. Polymeric Nanoparticles
Polymeric nanoparticles have multiple advantages in terms of biocompatibility, drug release, size control, and low toxicity [78]. Some of the most commonly used polymers for nanoparticles are poly(lactide-co-glycolide), poly(lactic acid), poly(ε-caprolactone), chitosan, and poly(alkylcyanoacrylates) [79]. Polymeric nanoparticles are most attractive in that there exist a large number of materials for nanoparticle synthesis. Different compositions of polymeric nanoparticles can be applied to encapsulate various drugs and deliver them to specific cellular surfaces. Application of polymeric nanoparticles in intravesical therapy has several advantages, such as increasing the retention time of drugs in the bladder, keeping higher local drug concentration, and reducing drug loss during urine discharge. Chitosan is a degradable, nontoxic, and natural polysaccharide isolated from the exoskeleton of crustaceans, and has been widely used as a biomaterial in humans [80–83]. Chitosan has three key properties that can improve intravesical delivery of drugs [84]. First, the polycationic charge and mucosadhesive property of chitosan promote adhesion to the negatively-charged bladder surface and hence increase the retention time of drug. Second, the high viscosity of chitosan solution protects itself from urine discharge. Third, chitosan can loosen gap junctions and enhance urothelial permeability [85]. Indeed, Ghosn et al. [86] reported that an imidazole-functionalized conjugate of polysaccharide chitosan (chitosan-IAA) can enhance the mucosal permeability and facilitate transepithelial delivery of optical contrast agents.

Modification of chitosan-based polymeric nanoparticles can also achieve improved encapsulation of drug and selective incorporation into bladder cancer cells. Bilensoy et al. [87] compared the delivery efficiency of the intravesical chemotherapeutic agent Mitomycin C (MMC) with three cationic nanoparticles of chitosan (CS), poly-epsilon-caprolactone coated with chitosan (CS-PCL), and poly-epsilon-caprolactone coated with poly-L-lysine (PLL-PCL). Their results showed that CS-PCL exhibited complete
drug release and was the most efficient formulation to encapsulate fluorescent markers. Most importantly, CS-PCL nanoparticles and MMC share hydrophilic properties; hence CS-PCL with a fluorescent marker were selectively incorporated into bladder cancer cells, but not by normal bladder cells.

4.4. Lipid Nanoparticles
There are two lipid nanoparticle systems that have been applied to cancer therapy, solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), both composed of lipid instead of phospholipid. SLNs have attracted interest in drug delivery by their specific advantages, such as stable structure, protection of labile drugs from degradation, controlled drug release, and specific targeting [88]. Furthermore, SLNs can encapsulate various drugs with diverse physicochemical properties [89–93]. However, the low drug loading of SLNs limits the control of drug release and undesirable drug expulsion during storage [94]. NLCs have been developed as the second generation of SLNs, which are composed of both solid and liquid lipids and hold the same advantages as SLNs. Importantly, NLCs show higher drug loading and less drug expulsion during storage [95]. To date, lipid nanoparticles have been applied to preclinical intravesical therapy. Kang et al. [96] showed that intravesical instillation of lipid nanoparticles which encapsulate p21-inducible double-stranded RNA can successfully deliver double-stranded RNA into tumoral tissue and induce p21 protein expression to further extend the survival of mice with established orthotopic bladder cancer. With the excellent properties of high drug loading and high tolerability, lipid nanoparticles may prove to be excellent pharmaceutical carriers in intravesical therapy against bladder diseases.

There are several important differences between these lipid nanoparticles and liposomes. (1) Structure: Lipid nanoparticles are vesicles with a single layer of lipid while liposomes are vesicles with two layers of lipid. (2) Composition: Lipid nanoparticles are composed of solid lipids (solid at room temperature) while liposomes are composed of phospholipids. (3) Drug leakage: Lipid nanoparticles show little drug leakage due to the solid matrix while liposomes can exhibit significant drug leakage. (4) Hydrolysis: Lipid nanoparticles are stable against hydrolysis of drug while liposomes are not. (5) Storage stability: Lipid nanoparticles are more stable than liposomes during storage [97].

4.5. Magnetically Responsive Nanoparticles
Magnetically responsive nanoparticles have been developed recently as novel drug vectors for cancer therapy and for diagnostic imaging [98, 99]. This type of nanoparticle is composed of magnetic elements such as iron, nickel, or cobalt, or chemical compounds. Magnetic nanoparticles can be directed and localized to specific tumor regions by administration of a magnetic field [100]. Magnetic nanoparticles with metallic cores can be coated with organic or inorganic shells to optimize the delivery of drugs to specific cell surfaces [13]. Doxorubicin is one chemotherapeutic reagent for intravesical treatment for bladder cancer [101] and it has also been well studied for drug delivery using magnetic targeted carriers [102]. Leakakos et al. [103] first demonstrated that magnetic nanoparticles with doxorubicin can be targeted and retained in specific regions of the bladder by administrating a magnetic field. In their study, the magnetic
nanoparticles were composed of metallic iron and activated carbon. Doxorubicin was absorbed into the activated carbon and iron core functions for magnetic susceptibility. This study demonstrated the feasibility to apply magnetic nanoparticles as pharmaceutical carriers in intravesical therapies.

5. DISCUSSION AND FUTURE PERSPECTIVES

Intravesical therapy is an adjuvant treatment after transurethral resection for superficial bladder cancer, while systemic therapy is typically for muscle-invasive or metastatic bladder cancer [104]. Figure 2 summarizes applications of various types of liposomes/nanoparticles as pharmaceutical carriers in the intravesical therapy against bladder diseases including superficial bladder cancer and PBS. New generations of intravesical treatments utilizing nanotechnology may not only advance the penetration of drugs but also deliver encapsulated molecules which cannot be absorbed by the urothelium. Most importantly, based on limited clinical studies [72, 76], these advances with nanotechnology may come without obvious side effects. By exploiting the versatile characteristics of nanoparticles, intravesical therapy efficacy can be improved in several directions. First, nanoparticles can be very beneficial to BCG therapy. Intravesical BCG is still the most efficient therapy against superficial bladder cancer.

Figure 2. Applications of liposomes/nanoparticles as pharmaceutical carriers in the intravesical therapy against bladder cancer. Variant liposomes can encapsulate small interfering RNA (siRNA), complementary DNA (cDNA), cytokines, or small peptides and be applied in intravesical therapy against bladder cancer. Many drugs against bladder cancer can also be encapsulated in different types of nanoparticles for intravesical treatments. Paclitaxel is a mitotic inhibitor used in cancer therapy, which can be encapsulated in protein nanoparticles. Mitomycin C is a conventional drug for bladder cancer, which can be loaded in polymeric nanoparticles to improve its therapeutic efficacy. Cytokine IL-12 can eradicate bladder cancer cells, which can be also encapsulated in polymeric nanoparticles for intravesical treatment. Doxorubicin is a drug widely used in many cancers, which can be loaded in magnetic nanoparticles for intravesical therapy against bladder cancer. p21-inducible double-stranded RNA can induce p21 protein expression which activates cell cycle arrest and apoptosis, and further extend the survival of mice with established orthotopic bladder cancer.
after TUR. Many positive and negative factors have been associated with the poor response of BCG therapy [105]. Activating or silencing these key genes involved in BCG-induced immune responses by using nanotechnology approaches is feasible to improve the BCG therapeutic efficacy. Second, PBS is still a mystery of bladder disease due to its unknown cause. Since many reports supported that liposomes could be an ideal solution against PBS, the customized liposomes could be designed based on individual symptoms and reach a better therapeutic result.

Nanoparticles have limitations, nevertheless. The toxicity of nanoparticles is indeed a concern during systemic therapy. However, little evidence can be found that intravesical nanoparticles/liposomes do or do not cause toxicity or side effects in animals or human patients. The reason may be that intravesical nanoparticles/liposomes do not directly contact the circulatory system. We still cannot exclude the possibility of toxicity induced by overdose of intravesical nanoparticles/liposomes, and more intravesical nanoparticle experiments are required for confirmation of their safety in humans.

6. CONCLUSIONS
Intravesical drug delivery is a preferred therapeutic approach against superficial bladder cancer due to several advantages over oral therapy, such as direct administration of drug on bladder lesions and reduced systemic side effects. However, intravesical therapy also has limited therapeutic efficiency due to factors such as bladder permeability barrier and bladder periodical discharge. Fortunately, the development of nanoparticles as pharmaceutical carriers in intravesical therapy overcomes the disadvantages of conventional intravesical therapy. Various types of nanoparticles have been well associated with bladder disease therapies, including superficial bladder cancer and PBS. Limited evidence mostly from animal studies supports that applications of nanotechnology in intravesical therapy may enhance the retention of drug in the bladder and drug permeability into bladder lesions. Furthermore, nanoparticles can carry some molecules which cannot actively transport into bladder lesions, such as small interfering RNA. Those outstanding strengths determine the dominant roles of nanoparticles in the next generation of intravesical therapy against bladder diseases. However, to reduce the risk of distant metastasis, the standard treatment for muscle-invasive bladder cancer is radical cystectomy instead of regional or systemic drug therapy. Therefore, the application of nanotechnology for bladder cancer is still focused on non-muscle invasive bladder cancer. Developing a better nanoparticle system which can deliver intact drugs/molecules to bladder urothelium without severe side effects is a goal for future therapy against bladder diseases.

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CONFLICT OF INTEREST
The authors indicated no potential conflicts of interest.

REFERENCES


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