

Nanotechnology as a tool to advance research and treatment of non-oncologic urogenital diseases

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Abstract: Nanotechnology represents an expanding area of research and innovation in almost every field of science, including Medicine, where nanomaterial-based products have been developed for diagnostic and therapeutic applications. Because of their small, nanoscale size, these materials exhibit unique physical and chemical properties that differ from those of each component when considered in bulk. In Nanomedicine, there is an increasing interest in harnessing these unique properties to engineer nanocarriers for the delivery of therapeutic agents. Nano-based drug delivery platforms have many advantages over conventional drug administration routes as this technology allows for local and transdermal applications of therapeutics that can bypass the first-pass metabolism, improves drug efficacy through encapsulation of hydrophobic drugs, and allows for a sustained and controlled release of encapsulated agents. In Urology, nano-based drug delivery platforms have been extensively investigated and implemented for cancer treatment. However, there is also great potential for use of nanotechnology to treat non-oncologic urogenital diseases. We provide an update on research that is paving the way for clinical translation of nanotechnology in the areas of erectile dysfunction (ED), overactive bladder (OAB), interstitial cystitis/bladder pain syndrome (IC/BPS), and catheter-associated urinary tract infections (CAUTIs). Overall, preclinical and clinical studies have proven the utility of nanomaterials both as vehicles for transdermal and intravesical delivery of therapeutic agents and for urinary catheter formulation with antimicrobial agents to treat non-oncologic urogenital diseases. Although clinical translation will be dependent on overcoming regulatory challenges, it is inevitable before there is universal adoption of this technology to treat non-oncologic urogenital diseases.

Keywords: drug delivery, nanocarriers, nanocarrier-based therapeutics, nanomedicine

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Introduction

The development of new technology often facilitates breakthroughs in scientific discovery, with concomitant advances in therapeutic modalities. This has been the case with nanotechnology applied to biomedical research, where a major focus for clinical translation has been toward optimizing its use for targeted drug delivery, imaging, diagnosis, and treatment.

Nanotechnology involves the understanding and control of matter and processes at the nanoscale dimension, a scale at which unique properties of

materials emerge that usually enables novel applications.¹ By definition, nanomaterials have sizes falling between 1 and 100 nm in at least one dimension, and when used as transport vehicles for another substance, they are referred to as nanocarriers. There are several types of nanocarriers with different compositions (organic, inorganic or hybrid) and structures that give them unique physicochemical properties and cargo capabilities.^{2–5} Examples of commonly used nanocarriers include liposomes, micelles, nanoparticles, carbon nanotubes and carbon dots, dendrimers, and nanogels. The great interest in

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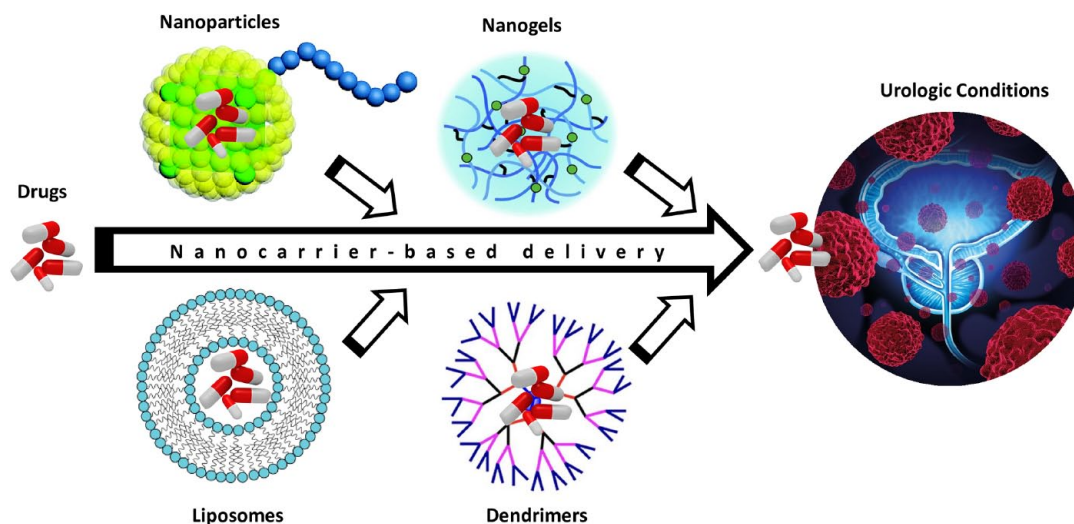


Figure 1. Nanocarrier-based delivery systems for targeted drug delivery.

using nanocarriers in biomedical research and therapeutics stems from their ability to surmount limitations faced with delivering drugs and biologicals using conventional administration routes, increasing the cargo's bioavailability, efficacy, and safety, particularly of those with low solubility, stability, tissue penetration, or that can cause off-target effects (Figure 1).

In the field of Urology, most of the research involving the use and development of novel nano-based drug delivery platforms has focused on cancer treatment. However, the potential application of nanotechnology in non-oncologic urogenital research and therapeutics is immense. Current management of erectile dysfunction (ED) and urinary bladder diseases relies mainly on oral medications that are not effective for all patients and can be accompanied by systemic side effects that reduce the patients' adherence to treatment. However, because the urogenital organs are easily accessible, they are highly amenable to topical delivery of therapeutics, as, for example, directly to the penile dermis or into the bladder by transurethral cannulation. These alternative routes have been explored and intravesical therapies are currently used to manage some bladder conditions. Nonetheless, delivery of therapeutics through these routes is also limited by natural obstacles. These include the remarkable barrier properties of the skin and the urothelium (the inner lining of the bladder) that make hard the penetration and absorption of dermally applied therapeutics, and dilution in the urine and wash-out with micturition of intravesically administered

therapeutics.⁶⁻⁸ However, these natural barriers can be overcome using nanocarrier-based delivery systems.⁸⁻¹⁰

The use of nanotechnology in urologic cancers (kidney, prostate, bladder) has been well-described and reviewed.¹¹ In comparison, its use in research, diagnosis, and treatment of benign urological conditions, which affects a large proportion of the population, has been limited. Therefore, the goal of this article is to provide an update on how nanotechnology, and in particular the development and use of nano-based delivery systems, is paving the way to advance basic and clinical research, and treatment of non-oncologic urogenital diseases. In this review, we will highlight the background, investigational approaches, and clinical status of nanocarrier-based therapeutics for ED, overactive bladder (OAB), interstitial cystitis/bladder pain syndrome (IC/BPS), and catheter-associated urinary tract infections (CAUTIs) (Table 1).

Materials and methods

PubMed/MEDLINE and Google Scholar databases were searched for relevant articles in the English language through 1 July 2021. Search strategy included the following terms: 'nanotechnology in urology' OR 'nanotechnology erectile dysfunction' OR 'nanotechnology overactive bladder' OR 'nanotechnology interstitial cystitis bladder pain syndrome' OR 'nanotechnology urinary tract infection'. The term 'nanotechnology' was also replaced with 'nanoparticle' and

Table 1. Overview of current and nanotechnology-driven therapeutics for non-oncologic urogenital diseases.

Non-oncologic urogenital disease	Current therapeutics	Challenges of current therapeutics	Nanotechnology-driven therapeutics	Advantages of nanotechnology-driven therapeutics	Challenges of nanotechnology-driven therapeutics
Erectile dysfunction	<ul style="list-style-type: none"> • PDE5 inhibitors • Intracorporal injections 	<ul style="list-style-type: none"> • PDE5 inhibitors can cause off-target effects including headache, nasal congestion, and dyspepsia • Patients with dysphagia have difficulty swallowing oral medications • Absorption pharmacokinetics of oral PDE5 inhibitors may be affected by eating and diet • Intracorporal injection can cause pain at the injection site, pain during erection, and hematomas 	<ul style="list-style-type: none"> • Topical NO-nanoparticles • Topical tadalafil/other PDE5 inhibitor nanoparticles • Topical PGE1-EE-nanoparticles • Papaverine-nanoparticles • Topical opiorphin-nanoparticles • SHH-PA-nanofibers • NGF-HA-nanoparticles • FL2-siRNA-nanoparticles • DHA-nanoemulsion • BIO 300 • Curcumin-nanoparticles 	<ul style="list-style-type: none"> • In general, nanotechnology allowing local, topical delivery of therapeutics (1) avoids the effects of eating and diet on absorption pharmacokinetics of orally administered agents, (2) avoids first-pass metabolism, potentially allowing for lower effective doses of therapeutics or the ability of poorly absorbed compounds to reach clinically relevant effective levels, (3) is less invasive, avoiding the need for swallowing or injection • Topical nitric oxide-releasing nanoparticles allow local, topical delivery of NO (impossible without nanotechnology) which induces an erectile response without affecting systemic blood pressure • Topical PGE1-EE/papaverine-nanoparticles, and topical opiorphin-nanoparticles modulate smooth muscle relaxation • SHH PA-nanofibers, NGF-HA-nanoparticles, FL2-siRNA-nanoparticles, and DHA-nanoemulsion promote nerve regeneration following radical prostatectomy • BIO 300 prevents radiation-induced erectile dysfunction following prostate cancer radiation therapy without sacrificing tumor radiosensitivity • Topically applied curcumin-nanoparticles allow greater absorption and bioavailability of curcumin than achieved by oral route, reaching systemic curcumin levels effective to improve erectile function, potentially through anti-inflammatory effects 	<ul style="list-style-type: none"> • Clinical translation from animal models to humans for all nanotechnology-driven therapeutics has been limited • IND approval would need to consider both bulk pharmacologic agent activities and potential novel physicochemical properties associated with their use at the nanoscale • Efficacy of PGE1-EE nanoparticles compared with established treatments (i.e., intracorporal injection) has not been investigated • Papaverine-nanoparticles have low bioavailability • Opiorphin-nanoparticles may result in priapism
Overactive bladder	<ul style="list-style-type: none"> • Oral anticholinergics • Intravesical antimuscarinics • Intravesical BoNT-A 	<ul style="list-style-type: none"> • Oral anticholinergics can cause dry mouth and constipation • Intravesical antimuscarinics has low retention in the bladder • Intravesical BoNT-A requires reinjections and has high rates of urinary retention, UTI, hematuria, and pain at the injection site 	<ul style="list-style-type: none"> • Lipo-BoNT • LP-encapsulated capsaicin • LP-encapsulated oligonucleotides • NO-nanoparticles • MBN-PEG-nanoparticle 	<ul style="list-style-type: none"> • Nanoparticle technology can potentially allow local intravesical delivery of anticholinergics to the bladder, reducing systemic side effects and increasing treatment compliance • Nanoparticle delivery systems can be engineered to increase indwelling time of therapeutics • Intravesical administration: <ul style="list-style-type: none"> • Lipo-BoNT reduces urinary frequency and urgency without increasing risk of urinary retention and UTI • Lipo-BoNT has high affinity for the urothelium without causing significant irritation • LP-encapsulated capsaicin attenuates bladder sensation, inhibits the micturition reflex, and decreases bladder overactivity • LP-encapsulated oligonucleotides decrease NGF expression and bladder overactivity • NO-releasing nanoparticles can reduce bladder contractions in those with sickle cell disease • MBN-PEG-nanoparticles increase MBN's bioavailability 	<ul style="list-style-type: none"> • Only Lipo-BoNT has reached clinical trials • MBN-PEG-NP toxicity has not been established

(continued)

Table 1. (Continued)

Non-oncologic urogenital disease	Current therapeutics	Challenges of current therapeutics	Nanotechnology-driven therapeutics	Advantages of nanotechnology-driven therapeutics	Challenges of nanotechnology-driven therapeutics
Interstitial cystitis/bladder pain syndrome	<ul style="list-style-type: none"> Behavioral modifications (e.g., avoidance of foods and fluids known to be bladder irritants) Anti-allergic and anti-inflammatory drugs Pain modulators Anticholinergics Botulinum toxin Oral medications (amitriptyline, cimetidine, hydroxyzine, pentosan polysulfate) Intravesical instillation of heparin, hyaluronic acid, or DMSO 	<ul style="list-style-type: none"> There is no single therapeutic agent and patients often require multimodal therapy Oral medications can cause nausea, constipation, dry mouth, weight gain, diarrhea, vomiting, and lightheadedness There is unclear optimal dose and frequency of dosing for intravesical drug instillation DMSO can cause pain upon instillation 	<ul style="list-style-type: none"> Empty LPs Lipo-BoNT Lipo-tacrolimus 	<p>Intravesical administration:</p> <ul style="list-style-type: none"> Empty LPs protect and repair the urothelial layer Empty LPs improve pain, urgency, and overall symptoms without treatment-related adverse events Lipo-BoNT improves suburothelial hemorrhage, recovers urothelial tight junction and adhesion proteins, decreases substance P release, and inhibits the overexpression of inflammatory mediators Lipo-tacrolimus increases tacrolimus' indwelling time and reduces the drug's systemic exposure, reduces bladder overactivity, and suppresses cyclophosphamide-induced bladder inflammation 	<ul style="list-style-type: none"> Only empty LPs and Lipo-BoNT have reached clinical trials For Lipo-BoNT in clinical trials, there was no difference in outcomes between the treatment and control groups
Catheter-associated urinary tract infections	<ul style="list-style-type: none"> Reduce use and duration of urinary catheters Urinary catheters coated with silver ions 	<ul style="list-style-type: none"> Patients with chronic urinary retention cannot reduce use and duration of catheterization Catheters coated with silver ions show mixed results in terms of efficacy and are not cost-effective when compared with standard catheters 	<ul style="list-style-type: none"> Catheters coated with silver, copper, and zinc-doped copper oxide as nanoparticles NO-nanoparticles 	<ul style="list-style-type: none"> Catheters coated with silver or zinc-doped copper oxide nanoparticles inhibit biofilm formation and bacterial growth Catheters coated with copper nanoparticles decrease antimicrobial activity by crossing bacterial cell membranes and damaging bacterial enzymes NO-nanoparticles prevent adhesion and biofilm formation of bacteria on catheters 	<ul style="list-style-type: none"> Clinical translation from animal models to humans for catheters coated with metal ions has been limited Translation of NO nanoparticles to preclinical animal models has been limited

BoNT-A, botulinum neurotoxin A; DHA, docosahexaenoic acid; DMSO, dimethyl sulfoxide; HA, hyaluronic acid; IND, Investigational New Drug Application; LP, liposomes; MBN, Mirabegron; NGF, nerve growth factor; NO, nitric oxide; PA, peptide amphiphile; PDE5, phosphodiesterase-5; PEG, polyethylene glycol; PGE1, prostaglandin E1; PGE1-EE, a PGE1 ethyl ester; UTI, urinary tract infection.

'nanocarrier' for each search term. Articles were considered eligible if they were written in the English language, were accessible via our university library services, and if the title was concordant with the content of our review. Reference lists of included articles and reviews were manually reviewed to identify additional relevant articles.

Erectile dysfunction

Background

ED is the inability to achieve or maintain an erection that is sufficient for satisfactory sexual performance. It affects at least 12 million men in the United States, with 52% of men aged 40–70 years experiencing some form of mild to moderate ED.^{12,13} A variety of factors (i.e. vascular, neurologic, psychological, hormonal) and conditions (i.e. diabetes mellitus, hypertension, hyperlipidemia, obesity, testosterone deficiency, prostate cancer treatment) can contribute to the development of ED.¹² The application of nanotechnology to organic ED has been the subject of several recent reviews.^{14–17}

Current therapeutics

The NO (nitric oxide)/cyclic guanosine monophosphate (cGMP) pathway is central to the development of an erectile response and is the target of phosphodiesterase-5 inhibitors (PDE5i), which represent the first-line therapy in the treatment of ED.¹⁸ Although these medications are typically safe and well-tolerated, a significant number of patients either cannot tolerate the side effects associated with PDE5i, such as headache, nasal congestion, and dyspepsia, or have difficulty swallowing medications (dysphagia).¹⁹ Also, given that the efficacy of PDE5i is dependent on the active production of NO from the endings of the cavernous nerve (CN), patients who do not generate sufficient NO because of CN damage resulting from surgical trauma (that accompanies radical prostatectomy) or chronic vascular inflammation (that occurs in diabetic patients) are often refractory to this treatment.

A more invasive yet efficacious therapy for ED is intracorporal injections. Prostaglandin E1 (PGE1, known commercially as alprostadil) is a potent vasodilator agent used to treat ED administered by direct intracorporal injection. It causes corporal smooth muscle relaxation by binding to PGE receptors, resulting in the activation of adenylate

cyclase and the subsequent accumulation of 3',5'-cAMP. Intracorporal injections have also been shown to commonly cause pain at the injection site, pain during erection, and hematomas/ecchymoses.²⁰ As a result, although intracorporal injections are efficacious, patients often prefer less invasive therapeutics, such as oral medications.²¹

Nanotechnology-driven therapeutics

Nanotechnology, and in particular the engineering of nanomaterials for target delivery of therapeutics, holds great potential to advance treatment for ED.

Targeting the NO/cGMP pathway. One of the first studies that explored the potential of a nanocarrier-based delivery system to treat ED demonstrated the feasibility of topical penile delivery of NO and a PDE5i (tadalafil) to improve erectile function outcomes in a rat model of aging.^{22,23} A hydrogel-derived nanoparticle was generated for these studies using a silane-based sol-gel technology synthesized from tetramethoxysilane (TMOS).^{23–31} Both the NO- and tadalafil-nanoparticles were applied as a gel to the glans and shaft of the rat penis, representing approximately 10 nmol NO (steady-state delivery) or 1 mg tadalafil, respectively.²³ An erectile response was observed in treated animals approximately 5 min after the administration of NO-nanoparticles and was followed by several other erections of diminishing intensity. It is important to note that over the 2-h time course of the experiments, there was no significant effect on systemic blood pressure, suggesting that the NO derived from the nanoparticles was acting locally. Furthermore, tadalafil is a PDE5i which maintains intracellular levels of cGMP after neuronal stimulation to induce an erection. Therefore, it was reasoned that after application of the tadalafil-nanoparticles, stimulation of the CN would be necessary to obtain an erectile response. Sixty minutes after topical application of tadalafil-nanoparticles to the glans of the penis, there was a significant improvement in the erectile response at a 4 mA level of stimulation compared with animals treated with 'empty' nanoparticles (which served as negative controls). More recently, sildenafil-nanoparticles were also tested in the aging rat model and were shown to improve erectile function after local topical application to the penile shaft.³²

The NO-nanoparticles were subsequently shown to also be effective at improving erectile function

outcomes in a rat model mimicking the nerve damage that occurs following radical prostatectomy.^{33,34} In one study, the NO-nanoparticles were applied topically to the penile shaft of a rat that had 2 weeks prior undergone bilateral CN transection. Following application, spontaneous erections were observed with a time of onset ranging from 5 to 37 minutes (with an average of 15 ± 11 minutes).³³ In another study, the topical application of NO-nanoparticles was combined with an oral PDE5i (sildenafil). Oral treatment with sildenafil resulted in no visible erectile response, but a combination of orally administered sildenafil with topical application of NO-nanoparticles produced significantly more spontaneous erections when compared with the NO-nanoparticles by themselves.³⁴

Modulate smooth muscle relaxation. Several studies have investigated the potential for transdermal delivery of a prodrug of PGE1 (a PGE1 ethyl ester, PGE1-EE) using 5% SEPA (soft enhancer of percutaneous absorption) in the formulation.^{35–37} The prodrug is hydrolyzed through the action of esterases present in the skin. However, these formulations are generally less efficacious than intracorporal injection. As an alternative, alcoholic nanoparticle hydrogels have been formulated, which could potentially act as efficient topical delivery vehicles of PGE1-EE.³⁸ In pharmacodynamic studies where the PGE1-EE hydrogels were applied to the penile dermis of cats, there was increased intracavernosal pressure compared with control nanoparticle hydrogels. However, the efficacy compared with direct injection has not been evaluated.

Papaverine hydrochloride is a direct-acting smooth muscle relaxant. Although its pharmacological mechanism of action is unclear, it is known to inhibit phosphodiesterases and may have direct actions on calcium channels. The normal route of administration is by intracorporal injection. Although several studies have described less invasive, transdermal approaches for its administration, the low bioavailability of these transdermal formulations has limited their efficacy and clinical translation.³⁹ Nevertheless, a recent study using a papaverine-nanoparticle formulation demonstrated improved transdermal delivery and therefore a potentially greater efficacy.⁴⁰ Specifically, the formula released 73% of its initial drug content within 2 h and the clinical evaluation showed an increase in the cavernous artery diameter and an increase in the peak systolic flow velocity.

Although an erection was not reported, the increased basal blood flow observed in these studies suggests it may be useful as a tool in penile rehabilitation following radical prostatectomy, where a primary goal is to maintain basal blood flow to prevent fibrosis and penile atrophy.⁴¹

Opiorphins are a family of peptides that act as neutral endopeptidase inhibitors and have been shown to play a role in relaxation of corporal smooth muscle tissue.⁴² The rat opiorphin homologue (sialorphin) encapsulated in silane-hydrogel nanoparticles when applied to the penile dermis of an aging rat model of ED resulted in a prolonged erectile response (increased ICP/BP ratio in the absence of CN stimulation that lasted for 8 min) with an average onset time of 4.5 min after application.²³ The opiorphin family of peptides have been associated with priapism,⁴³ and the prolonged erectile response observed in rats may raise concerns that a treatment based on opiorphin-nanoparticles may elicit priapism in patients if the release of opiorphin from nanoparticles is not carefully regulated.

Promote nerve regeneration following radical prostatectomy. One of the first reports exploring the application of nanomaterials to enhance nerve repair involved the delivery of sonic hedgehog (SHH) applied to the site of CN injury in a rat animal model. The rationale for focusing on SHH was provided by findings demonstrating that intracorporal injection of the SHH protein at the time of CN injury decreased injury-induced apoptosis in a dose-dependent manner.⁴⁴ SHH was incorporated into aligned peptide amphiphile (PA) nanofibers, which consist of a hydrophilic peptide with attached lipid chains that self-assemble into structures with a high aspect ratio of nanofibers.^{45–47} The SHH PA-nanofibers were applied to the site of CN injury in a rat model, and 6 weeks later, the animals' erectile function was evaluated by cavernosometry.^{48,49} Animals treated with SHH PA-nanofibers had improved erectile function (as determined by increased ICP/BP ratio following electrical stimulation of the CN) accompanied by improved penile architecture.⁴⁸ Subsequent reports using the same animal model reported that treatment with the SHH PA-nanofiber reduces penile apoptosis and fibrosis^{50,51} and promotes regeneration of CN fibers.^{48,52}

Investigations on the potential of nerve growth factor (NGF) to improve erectile function

following nerve injury have a long history.⁵³ However, if applied at the time of injury, or through intracorporal injection, NGF has a short half-life at the target site. To circumvent this limitation, an extended-release NGF formulation was developed where NGF was encapsulated into a hyaluronic acid (HA) hydrogel nanoparticle. In one such formulation, 20% of the loaded NGF is released over 35 days. Another potential advantage of this formulation is that HA binds to specific proteins on the cell surface which may tether the nanoparticles to the site of application.⁵⁴ In a rat model of CN injury, animals treated with the NGF-HA-nanoparticle at the time of injury showed approximately 40% better erectile function (determined by ICP/BP) than untreated controls. Improved erectile function was associated with reduced smooth muscle atrophy and increased endothelial nitric oxide synthase (eNOS) expression in penile tissue. Interestingly, there was a synergistic effect when treatment of the NGF-HA-nanoparticles was combined with human adipose-derived stem cells (hADSC). It was speculated that the HA component of the nanoparticle may anchor hADSCs at the site of application and provide a microenvironment for neuronal differentiation of the hADSC.

The ability of nanoparticles to anchor or target stem cells to the site of CN injury has been more directly investigated in two studies.^{55,56} Rat ADSC (rADSC) were magnetized with NanoShuttle, a commercially available biocompatible magnetic nanoparticle assembly consisting of gold, iron oxide, and poly-l-lysine (from n3D Biosciences, Inc., Houston, TX, USA). Following CN crush, NanoShuttle-rADSC were injected into the corpora cavernosa and two neodymium magnets were placed outside of the corpora cavernosum of the penis for 6 h. Cell tracking showed that the NanoShuttle-rADSC were successfully retained at the corpora cavernosa for 3 days, while control rADSC were washed out after 1 day. Four weeks after injury, erectile function (determined by ICP/BP) was significantly higher in animals treated with NanoShuttle-rADSC than in control animals. Improved erectile function correlated with the level of expression of two markers of erectile function [α -smooth muscle actin and platelet endothelial cell adhesion molecule (PECAM-1)] in the corpora cavernosa.

Docosahexaenoic acid (DHA) has well-documented anti-inflammatory and antioxidant

activities as well as neuroprotective properties. In a rat CN crush model, animals were administered a single intraperitoneal dose of either vehicle or a DHA-nanoemulsion at 10, 50, or 250 $\mu\text{g}/\text{kg}$.⁵⁷ At 28 days post-injury, erectile function (determined by ICP/BP) was significantly higher in all groups receiving the DHA-nanoemulsion than in the vehicle group, though was most pronounced in animals receiving 50 $\mu\text{g}/\text{kg}$. The improved erectile function following DHA-nanoemulsion treatment was associated with increased expression of neuronal nitric oxide synthase (nNOS), axon numbers, and smooth muscle cell content.

Studies have also investigated the potential of a microtubule regulator, termed Fidgetin-like 2 (FL2), to promote CN regrowth following injury. Targeted FL2 depletion via topical application of FL2-siRNA encapsulated in silane-hydrogel nanoparticle formulations (FL2-siRNA-nanoparticle) has been shown to promote the closure and repair of cutaneous wounds in a mouse model.⁵⁸ More recently, in a rat model of CN crush or transection injury, it was reported that when FL2-siRNA-nanoparticle was applied at the time and site of injury, there was an improved erectile response (determined by ICP/BP) compared with controls beginning at 2 weeks post-treatment.⁵⁹ Potentially, from a translation point, application of this formulation at the time of prostatectomy could bring dual benefits by combining CN regeneration with an overall increase in the rate of wound healing.

Prevent radiation-induced ED following prostate cancer radiation therapy. More than half of the patients who receive radiation therapy (RT) for prostate cancer will develop radiation-induced erectile dysfunction (RiED) within 3–5 years after treatment.⁶⁰ One study used rat models to investigate whether BIO 300, a synthetic nanosuspension of genistein (naturally occurring soy isoflavone that serves as an estrogen receptor beta selective agonist), improves the therapeutic index in prostate cancer treatment by preventing RiED without sacrificing tumor radiosensitivity. Investigators found that BIO 300 did not protect tumors from RT-induced cytotoxicity but prevented RiED when administered 3 days before RT and daily for up to 2 weeks post RT, and also reduced the development of RiED when administered 2 h after starting RT.⁶¹ Therefore, if translated to clinical studies, this novel nanotechnology-based approach may offer an alternative therapeutic modality to preserve erectile function in men with

prostate cancer undergoing RT while maintaining tumor response to RT.

Modulation of diabetic inflammatory response. Systemic inflammation is linked to the development of ED in those with diabetes.⁶² Several studies in animal models have demonstrated the potential of oral administration of curcumin (a naturally occurring compound, which has anti-inflammatory, anti-oxidative stress, and anti-catabolic activity) to treat ED associated with diabetes.^{63–66} However, clinical translation of curcumin-based therapies has been limited because of its low oral bioavailability, poor aqueous solubility, and rapid degradation. Some of these shortcomings could be mitigated when curcumin is encapsulated into a silane-hydrogel nanoparticle (curcumin-nanoparticle) which allows slow and sustained transdermal delivery of curcumin, thereby avoiding first-pass metabolism.⁶⁷ In studies with a rat model of type II diabetes, it was shown that curcumin-nanoparticles penetrate the abdominal epidermis and persist in hair follicles for at least 24h.⁶⁷ Diabetic animals treated with curcumin-nanoparticles, compared with animals treated with blank nanoparticles, exhibited higher average ICP/BP following CN stimulation, reaching statistical significance at 0.75 mA. This study showed that there was also an effect of curcumin-nanoparticle treatment on inflammatory markers in the diabetic rat corporal tissue. For example, NF-activating protein (NFKAP) expression was decreased by 60% and heme oxygenase-1 (HO-1) expression was increased by 60% in curcumin-compared with blank-nanoparticle-treated animals.⁶⁷ The mechanism underlying the improvement in erectile function following curcumin-nanoparticle treatment was not determined in these experiments. However, the fact that ICP/BP values were inversely correlated with NFKAP, and directly correlated with HO-1 expression in corporal tissue, suggests a reduction in local inflammation may be one of the mechanisms by which curcumin-nanoparticles improve erectile function in diabetic rats.

Benign bladder dysfunction

Patients with non-oncologic bladder conditions, such as OAB and IC/BPS, are treated with oral and intravesical medications, and ultimately surgery if they do not respond to or cannot tolerate the standard treatment options. Oral medications often produce off-target effects and intravesical uptake of therapeutics is often limited by the tight

permeability barrier formed by the umbrella cells that line the luminal surface of bladder and by the reduced dwelling time of drugs in the bladder lumen.⁶⁸ Nanotechnology provides a platform for development of more efficient and bladder-targeted drug delivery systems that can circumvent these limitations and significantly advance management of these bladder conditions. Unlike studies in ED, in which the potential of nanocarrier-based therapeutics has only been investigated in animals, use of this technology for pathologies related to benign bladder dysfunction has been investigated at both preclinical and clinical levels.

Overactive bladder

Background

OAB is defined by the International Continence Society as a storage symptom syndrome of urgency, with or without urgency urinary incontinence, which is usually accompanied with increased daytime frequency and nocturia.⁶⁹ Approximately 3–46% of the population is affected by OAB, with a higher prevalence among women and the elderly. It is associated with a significant decrease in a patient's quality of life.⁷⁰

Current oral and intravesical therapeutics

The mainstay treatment for patients with OAB is anticholinergic pharmacotherapy. However, oral use of these drugs is associated with considerable adverse side effects such as dry mouth and constipation that often result in poor patient compliance.⁷¹ Conversely, intravesical administration of antimuscarinics has been reported to result in less frequent and less intense side effects.^{72–78} However, despite its efficacy and safety, intravesical treatment with antimuscarinics also has shortcomings. An important one is the unavoidable drug dilution and low retention in the bladder caused by urine buildup and voiding, entailing the need for frequent catheterizations. In this regard, this route of treatment would only be ideal for patients who already perform clean intermittent catheterization (CIC).

The development of intravesical treatment with botulinum neurotoxin A (BoNT-A) circumvented some of the limitations faced with use of anticholinergics. BoNT-A is a neurotoxin that binds with high affinity to the synaptic vesicle proteins of peripheral cholinergic nerve endings

and inhibits neuromuscular and parasympathetic signaling by preventing release of acetylcholine into the synapse. Like antimuscarinics, BoNT-A inhibits detrusor contractions by targeting the bladder cholinergic system. However, because BoNT-A is directly injected into the detrusor muscle, it has the advantage of not only acting locally but also lasting longer, for about 6–8 months.⁷⁹ However, BoNT-A intravesical treatment also requires reinjections to maintain treatment efficacy and have been associated with considerable rates of urinary retention, UTI, hematuria, and pain at the injection site.^{80,81}

Nanotechnology-driven therapeutics

Improving intravesical BoNT-A and capsaicin drug delivery. Use of liposomes (LP) to encapsulate and deliver BoNT-A through intravesical instillation has been tested in rats and shown to provide an efficient and alternative approach for BoNT-A delivery without bladder wall injection. Liposomes are self-assembled vesicles formed by synthetic or natural phospholipid bilayers that enclose an interior aqueous space. This unique structure allows encapsulation and transport of lipophilic cargos within the lipid bilayer and/or hydrophilic cargos in the aqueous compartment. Since the lipidic bilayer structure of LPs is similar to that of biological membranes, they can easily adhere to the cell surface and deliver their cargos by endocytosis. The liposomal BoNT-A (lipo-BoNT) thereby displayed high affinity for the urothelium without causing significant irritation.⁸² A subsequent study investigated the use of lipo-BoNT in 24 OAB patients in a single-center, double-blind, randomized, parallel controlled trial. At 1 month, the lipo-BoNT group had a significant improvement in urinary frequency and reduction in urgency episodes when compared with the control group (treated with normal saline). Importantly, the treatment was well-tolerated with no significant adverse events related to lipo-BoNT or the instillation procedure.⁸³ Moreover, a multicenter, double-blind, randomized, placebo-controlled study enrolled 62 patients with OAB, who were refractory to anticholinergic oral medications, and found that at 1 month, the lipo-BoNT group had significant reductions in urinary urgency when compared with the control group. Similar to the previous study, lipo-BoNT was concluded to be safe as there was no increased risk of urinary retention and UTI.⁸⁴ Therefore, these studies have further supported lipo-BoNT to not only be efficacious in reducing OAB symp-

toms, but also to be safer than BoNT-A intravesical injections.

Intravesical administration of capsaicin, the pungent ingredient in red pepper, has been studied in rats as an approach to manage OAB by desensitizing the afferent C-fibers, thereby resulting in a decrease in the micturition reflex and bladder overactivity. Because capsaicin is hydrophobic, intravesical administration of capsaicin involves normal saline solution with 30% ethanol. However, the high ethanol concentration has been shown to induce histological epithelium thinning and submucosal edema.⁸⁵ In order to avoid solubilizing capsaicin through ethanol, one study encapsulated capsaicin within the hydrophobic core of LPs prior to intravesical instillation. Findings from this study demonstrated that intravesical treatment of rats with LP-encapsulated capsaicin resulted in complete blockage of the micturition reflex without any adverse histological changes.⁸⁶

Using antisense oligonucleotides to downregulate NGF expression. Overexpression of NGF in the rat bladder has been shown to cause hyperexcitability of C-fiber sensory pathways, subsequently contributing to OAB symptoms.⁸⁷ Currently, downregulation of NGF is encouraged through intravenous administration of monoclonal human NGF antibodies. Although these antibodies have been shown to be effective in relieving lower urinary tract symptoms, off-target effects resulted in considerable rates of paresthesia, hypoesthesia, and arthralgia.⁸⁸ One study investigated local downregulation of NGF in the rat bladder through intravesical delivery of antisense oligonucleotides.⁸⁹ Since the oligonucleotides were not able to penetrate the urothelium barrier and therefore to not exert their effects, the investigators encapsulated the oligonucleotides into LPs. As a result, the LP-encapsulated oligonucleotides were not only able to penetrate the urothelial cells, but also to significantly decrease NGF expression and bladder overactivity while avoiding off-target effects.⁸⁹

Targeting the NO and RhoA/Rho-associated kinase pathway. The prevalence of OAB in patients with sickle cell disease (SCD), an inherited disorder characterized by an abnormal structure of one of the globin chains of the Hb molecules, can be as high as 40%.⁹⁰ Physiologically, SCD patients are susceptible to experiencing OAB symptoms as SCD creates a state of chronic low bioavailability

of NO that is accompanied by dysregulation not only of NO signaling but also of the RhoA/ROCK-signaling pathways, which have been proposed to contribute to detrusor overactivity and urethral dysfunction.^{91,92} A recent study explored the potential use of intravesical delivery of NO-releasing nanoparticles (NO-NPs) to improve bladder function in transgenic SCD mice.⁹³ This study demonstrated that intravesical NO essentially reversed the OAB phenotype in SCD mice. The frequency of voiding and non-voiding bladder contractions was reduced in NO-NP-treated SCD mice and the molecular imbalance observed in the NO and RhoA/ROCK signaling pathways was corrected when compared with wild-type mice.⁹³

Optimizing oral drug delivery. Mirabegron (MBN) is a sympathomimetic β -3 adrenergic receptor agonist used to orally treat OAB. However, the first-pass metabolism effect, low water solubility, and MBN high protein binding diminish its bioavailability. A study recently sought to increase MBN's oral bioavailability by encapsulating MBN into polyethylene glycol nanoparticles (MBN-PEG-NP).⁹⁴ The MBN-PEG-NP were prepared through the pre-emulsion ultrasonication method and then evaluated for particle size, zeta potential, entrapment efficiency, and *in vitro* release. After optimization, MBN-PEG-NP were given orally to rats. Investigators found that the bioavailability of MBN-PEG-NP was twofold greater than the bioavailability of MBN without PEG-NP. These findings suggest that the nanoparticles were absorbed through intestinal lymphatics since they resembled chylomicrons in the gut, which would reduce the MBN first-pass metabolism effect.⁹⁴ Although novel and exciting, additional studies are warranted to investigate the drug's toxicity since its clearance and distribution have been altered once encapsulated in PEG-NP.

Interstitial cystitis/bladder pain syndrome (IC/BPS)

Background

The Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction characterizes IC/BPS as an unpleasant sensation in the bladder consisting of pain, pressure, or discomfort that is longer than 6 weeks and does not have a clear identifiable cause.⁹⁵ Like OAB, IC/BPS can significantly decrease quality of life and is more prevalent in women than in men, affecting

2.7–6.5% of women versus 2.9–4.2% of men.^{96,97} There are no objective diagnostic tests and cystoscopic findings are nonspecific. Therefore, diagnosis of IC/BPS is based on subjective patient-reported symptoms.^{96,98}

Current therapeutics

The etiology of IC/BPS is not entirely known. Among possible triggers are infection, autoimmune response, allergic reaction, neurogenic inflammation, urothelial dysfunction, and genetic predisposition.⁹⁸ Because of its multifactorial nature, various therapeutic approaches are recommended to manage IC/BPS, with the main goal of maximizing symptom control and patient quality of life while minimizing adverse events and patient burden.^{99,100} Unfortunately, there is no single therapeutic agent for IC/BPS and patients often require conservative therapeutic approaches that include behavioral modifications (e.g. avoidance of foods and fluids known to be bladder irritants), use of anti-allergic and anti-inflammatory drugs, pain modulators, anticholinergics, botulinum toxin, and drugs that protect the bladder mucosa. Bladder distension, neuromodulation, and surgical interventions are recommended when all other treatments fail to control symptoms within an acceptable level.

Oral medications commonly used to manage IC/BPS symptoms, including amitriptyline, cimetidine, hydroxyzine, and pentosan polysulfate [only one that is Food and Drug Administration (FDA)-approved], have shown limited efficacy and conflicting evidence supporting their therapeutic effect. In addition, these medications have well-documented undesirable side effects such as nausea, constipation, dry mouth, weight gain, diarrhea, vomiting, and lightheadedness that are in some cases seen in about 80% of patients.¹⁰¹ Intravesical drug instillation is another route of drug administration and is generally more effective than oral medications. Some intravesical drugs, such as heparin and hyaluronic acid, aim at reconstituting the glycosaminoglycan (GAG) layer of urothelium, which is proposed to be impaired in patients with IC/BPS.^{102–104} Due to its anti-inflammatory and analgesic effects, dimethyl sulfoxide (DMSO) is the most common and only FDA-approved intravesical medication. However, unclear optimal dose and frequency of dosing combined with pain upon instillation makes DMSO an unattractive therapeutic agent.¹⁰¹

Nanotechnology-driven therapeutics

Protecting and repairing the urothelial layer with empty liposomes. The first studies exploring the application of nanotherapeutics in IC/BPS focused on investigating the effects of intravesical treatment with LPs composed only by phospholipids ('empty' LPs).¹⁰⁵ These studies were based on the ability of LPs to form a molecular film on cell surfaces and were further motivated by reports describing the healing and regeneration properties of topically applied empty LPs in the treatment of ophthalmic conditions.^{105,106} One of these early preclinical studies revealed that intravesical instillation of empty LPs protected against irritants (including potassium chloride, protamine sulfate, and acetic acid), indicating an increase in the urothelial barrier properties.¹⁰² When tested in humans, a study with 14 patients with IC/BPS showed that intravesical treatment with empty LPs composed of sphingomyelin resulted in significant improvements in pain, urgency, and overall symptoms without treatment-related adverse events.¹⁰⁷ A subsequent clinical study with 24 patients with IC/BPS evaluated the safety and efficacy of empty LPs when compared with oral pentosan polysulfate.¹⁰⁶ Both treatments were reported to result in comparable efficacy in reducing the IC/BPS symptoms of urinary frequency, nocturia, pain, and urgency. The mechanism of action of empty LPs in the bladder still remains to be fully elucidated, but their beneficial effect likely results from the combined protective action of the physical coating of the urothelium and the anti-inflammatory properties of sphingomyelin that would promote repair and regeneration of the bladder lining.¹⁰⁵

Improving intravesical BoNT-A and tacrolimus drug delivery. As with OAB, BoNT-A is also used for treating IC/BPS.^{99,108} The mechanism underlying the reported effects of BoNT-A in ameliorating IC/BPS symptoms seems to involve not only the inhibition of synaptic release of acetylcholine that reduces detrusor overactivity but also the blockade of release of pro-inflammatory neurotransmitters, such as substance P and calcitonin gene-related peptide (CGRP). A recent preclinical study evaluated the use of lipo-BoNT for the treatment of Ketamine-induced cystitis in rat models.¹⁰⁹ The investigators observed that intravesical lipo-BoNT improved suburothelial hemorrhage, recovered urothelial tight junction and adhesion proteins, decreased substance P release in the urothelium, and inhibited the overexpression of inflammatory mediators.¹⁰⁹ Although

findings from this study using lipo-BoNT to treat Ketamine-induced cystitis in a rat model were promising, using lipo-BoNT to treat refractory IC/BPS in humans revealed conflicting results. A multicenter, double-blind, randomized control trial used lipo-BoNT to treat 96 patients with refractory IC/BPS. Although lipo-BoNT was well-tolerated and improved symptoms of IC/BPS, there was no difference in outcomes between the treatment and control groups. The investigators hypothesized that this may be due to lipo-BoNT not being able to penetrate the detrusor deep enough as it would through injection.¹¹⁰

Hemorrhagic cystitis is commonly observed as a side effect in patients undergoing chemotherapy with cyclophosphamide/ifosfamide or pelvic radiation therapy. Tacrolimus, a potent hydrophobic immunosuppressant, helps treat hemorrhagic cystitis by interfering with interleukin-2-dependent T-cell activation through the inhibition of calcineurin phosphatase.¹¹¹ However, treatment with this drug is accompanied by serious systemic side effects, including neurotoxicity, nephrotoxicity, and hypertension, and intravesical administration is made difficult by its high hydrophobicity. To circumvent these problems, the potential use of liposomes to deliver tacrolimus through intravesical instillation was explored in a study conducted with an animal model of cyclophosphamide-induced cystitis.¹¹² Findings from this study demonstrated that intravesical instillation of liposome-encapsulated tacrolimus (lipo-tacrolimus) reduced bladder overactivity and suppressed cyclophosphamide-induced bladder inflammation in rats, reducing the expression of prostaglandin E receptor 4 (EP4) and normalizing the levels of interleukin 2 and PGE₂ in the bladder tissue and urine.¹¹² A subsequent study evaluated the pharmacokinetics of lipo-tacrolimus in rats and reported that a single intravesical lipo-tacrolimus administration of 200 µg/ml can produce active drug levels in the bladder for 24h, therefore increasing its residence time while also significantly decreasing systemic exposure.¹¹³ Furthermore, a more recent study examined using lipo-tacrolimus to treat radiation-induced cystitis in rats.¹¹⁴ Four weeks after receiving radiation, the rats were treated with a lipo-tacrolimus instillation and the investigators observed that the inter-micturition interval, which significantly decreased after radiation, returned to baseline after treatment. In addition, histology of the lipo-tacrolimus-treated bladder was identical to a normal bladder, whereas the control group showed changes associated with cystitis.¹¹⁴

Using antisense oligonucleotides to downregulate NGF expression. Several studies have reported elevated urinary levels of NGF in patients with IC/BPS that would originate from its upregulated expression and release from bladder urothelial and detrusor smooth muscle cells.^{115–118} Urinary NGF levels have been shown to correlate with the severity of pain and urgency symptoms and proposed to play a role in IC/BPS pathophysiology by sensitizing the bladder afferents, causing bladder overactivity and nociceptive responses.^{119–122} One study examined the potential of using liposomes for intravesical delivery of NGF antisense oligonucleotides (LP-OND) in a rat model of IC/BPS induced by intravesical instillation of hydrogen peroxide.¹²³ In this animal model, IC/BPS-like symptoms are evident as increases in micturition, freezing behavior (motionless head turning toward lower abdomen), bladder weight, infiltration of inflammatory cells, submucosal bladder bleeding, and NGF protein overexpression. After intravesical administration of LP-OND, all the above-mentioned findings significantly improved.¹²³ The study also observed that LPs delivered the NGF antisense OND into the urothelium and not the detrusor, suggesting that urothelium NGF alone may be contributing to IC/BPS.¹²³ Therefore, if translated to clinical studies, use of nanocarriers to modulate the expression of urothelial NGF may prove to be highly beneficial to manage not only OAB but also IC/BPS symptoms.

Catheter-associated UTIs

Background

Urinary catheterization (UC) is a common healthcare procedure. Up to 25% of hospitalized patients have an indwelling urinary catheter placed sometime during their hospital stay, and about 10% of all residents receiving care in nursing homes live with an indwelling catheter.^{124,125} UC is also the treatment of choice for individuals with difficulty in emptying their bladders due to neurogenic and non-neurogenic causes. For those patients, intermittent self-catheterization is the optimal procedure, but many individuals also require short- or long-term use of indwelling catheters. The major concern with UC is the associated risk of UTIs. UTIs are the most common type of healthcare-associated infection reported to the National Healthcare Safety Network (NHSN). UTIs account for about 40% of nosocomial infections, and about 80% of these are CAUTIs.^{126,127} The pathogenesis of CAUTIs

relates mainly to the susceptibility of the catheter materials to bacterial colonization and biofilm formation.¹²⁸ The presence of bacterial biofilm also complicates the treatment of CAUTIs. The biofilm protects the bacteria, and minimal concentrations of antibiotics required to combat the bacteria embedded in the biofilm may be 101–104 times higher than against the planktonic bacteria.¹²⁹ The emergence and spread of multidrug resistant bacteria are thus constant concerns with the treatment of CAUTIs.

Current therapeutics

Current approaches to reduce the risk of CAUTIs are limited and are based mainly on recommendations to reduce urinary catheter use and duration of use in all patients, which is not always possible, particularly in individuals who require chronic catheterization. Research efforts have thus focused on identifying antimicrobial agents that can be used other than antibiotics, and novel catheter materials and coatings that can deter the formation of bacterial biofilms. Silver ions are the most extensively studied catheter coatings. By the release of silver ions into the bladder after catheter placement, oxidative stress is induced, which disrupts bacteria's cell membrane and proteins.¹³⁰ However, animal studies and clinical trials showed mixed results in terms of efficacy and were not cost-effective when compared with nitrofurazone-coated catheters, silicone catheters, and other standard catheters.^{131–136} Translation to the clinic falls short due to several factors, but for the most part, due to the lack of testing in animal models of CAUTIs. Catheterization changes the bladder environment generating ideal conditions for bacterial colonization.^{137–139} Antimicrobial agents may also indirectly alter the bladder environment, the bladder function, and the bladder responses to infection. Unfortunately, *in vitro* studies cannot simulate these changes or indirect effects of treatment, neither can they account for the complexity of the host–catheter–microbe interactions.

Nanotechnology-driven therapeutics

Decreasing antimicrobial activity through catheters with metal-coated nanoparticles. Coating catheters with silver, copper, and zinc-doped copper oxide (CuO) as nanoparticles have been investigated. Silver nanoparticles have the same mechanism of action as mentioned above, and although studies have shown catheters coated with silver nanoparticles to inhibit biofilm formation and

growth of several bacteria when compared with uncoated catheters, inflammation and toxicity assessment are limited due to the lack of testing in animal models of CAUTIs.^{140,141} Copper nanoparticles decrease antimicrobial activity by crossing bacterial cell membranes and then damaging bacterial anti-apoptotic enzymes.¹⁴² An *in vitro* study investigated the antimicrobial activity of copper nanoparticles against *Escherichia coli* and found that by 2 min after the bacteria incubation with the copper nanoparticle-coated catheter, no viable bacteria was recovered.¹⁴³ Furthermore, zinc-doped CuO nanoparticles, whose antimicrobial mechanism is currently under investigation, have been investigated in one study with rabbit models of CAUTIs.¹⁴⁴ The study observed that after rabbits were catheterized with uncoated and coated catheters, and infected for 7 days, there was a significant reduction in bacterial biofilm formation. In addition, urine samples, which were collected throughout catheterization, revealed lower bacteria formation in animals catheterized with the Zn-doped CuO-coated catheter.¹⁴⁴ Although the results from these early studies are quite promising, clinical trials are needed to assess toxicity.

Delivery of NO through nanoparticles. NO is well-known for its broad-spectrum antifungal and antibacterial activity.^{32,33} Increased inducible NOS (iNOS) activity and nitrite levels have been documented in the bladder and urine of patients suffering from UTI. NO has therefore been suggested to play an important role in development and host response to UTIs.^{145,146} Intravesical use of NO, instead of conventional antibiotics to treat and prevent CAUTI, would be advantageous given its broad-spectrum bactericidal activity without risk of developing multidrug resistant (MDR) bacteria. NO, however, is a highly reactive gas proven to be difficult to deliver conveniently, and this has largely precluded its clinical use, even in hospital settings. NO-delivering systems, such as NO nanoparticles, have proven ideal in circumventing this limitation. Studies have shown that NO nanoparticles interfere with or prevent adhesion and biofilm formation of *Staphylococcus aureus* and *Candida albicans* on intravenous catheters using rodent models of implanted catheters.^{147,148} Moreover, moieties that can be included in the nanoparticle composition, like chitosan, can further disrupt biofilms formed on intravenous catheters.^{149,150} However, testing of their therapeutic potential in preclinical animal models of CAUTI has not been performed and represents a major barrier to clinical translation. Nevertheless, there

are currently ongoing studies to evaluate nanoparticles for sustained and controlled intravesical NO release in animal models that mimic the conditions encountered by catheterized patients.

Additional potential usage of nanoparticles for benign urogenital pathologies

There have been significant advancements in the use of nanocarrier therapeutics for ED, OAB, IC/BPS, and CAUTIs because of the accessibility of the organs involved in these pathologies. Topical and intravesical application of nanocarrier-based therapies allows for a minimally invasive approach that is difficult to achieve for other benign urogenital pathologies, such as benign prostatic hyperplasia (BPH), due to anatomical barriers. As a result, a more invasive modality would have to be implemented to evaluate the potential benefits of using nanocarriers for such anatomically constrained conditions.

Nevertheless, two recent animal studies have investigated the use of nanoparticles in treating BPH. One study evaluated the effect of intraperitoneal injection of 50 and 20 nm gold nanoparticles (AuNps) in a rat model of testosterone-induced BPH.¹⁵¹ Interestingly, findings from this study show size-dependent effects of AuNps treatment on BPH progression. While the 20-nm AuNps treatment inhibited prostatic cell proliferation, inflammation, and angiogenesis and ameliorated BPH, treatment with 50 nm AuNps enhanced prostatic inflammation and hyperplasia.¹⁵¹ The other recent animal study used the ablative properties of laser nanoparticles (hyperthermia technique) to successfully irradiate and induce apoptosis of prostatic tissue in the rat model of testosterone-induced BPH.¹⁵² However, since both studies failed to extensively evaluate the toxicity of nanoparticles on prostatic tissue, additional preclinical validation is needed before beginning clinical studies.

Discussion

There is increasing awareness and utilization of nanotechnology as a tool to advance basic and clinical research in the field of non-oncologic urogenital disease that is paving the way for development of novel therapeutic approaches (Figure 1, Table 1). Indeed, compared with diseases afflicting internal tissues and organs, urogenital diseases are often more amenable to nanocarrier-based therapeutics given the easy

and direct access of urogenital organs by intravesical or transdermal administration. However, some specific barriers in applying this technology to urogenital disease arise from the dilution and washout of intravesically delivered therapeutics and transdermal penetration depth of topically applied nanocarriers. These drawbacks can be addressed by modifying the physicochemical composition of the nanocarriers and tailoring them for their intended target. For example, nanocarriers can be decorated with ligands that can recognize the target cell surface or include paramagnetic nanomaterials in its composition to target and hold the nanocarriers in place through externally applied magnets.^{153–155}

In general, the use of nanocarriers to deliver therapeutic agents has several advantages over conventional drug administration routes. They allow local and transdermal applications of therapeutics that can bypass the first-pass metabolism associated with an oral route and improve drug efficacy through encapsulation of hydrophobic drugs, thereby lowering the effective therapeutic dose and reducing systemic toxicity. Furthermore, nanocarriers can allow for a sustained and controlled release of encapsulated agents. Most nanomaterial-based delivery vehicles are also highly malleable, such that they can deliver a great variety of therapeutic agents (including nucleic acids, naturally occurring and synthetic organic and inorganic therapeutics, and even gaseous compounds, such as NO), and formulations are relatively easily modified to change the release kinetic of therapeutic agents (Table 1).

In any disease and therapeutic focus area of investigation, studies with animal models of human diseases have been an instrumental and essential step in the research process before conducting clinical trials and translating findings to patients. However, it has become increasingly evident that conclusions made based on preclinical studies cannot be directly transferred to human studies, as inherent species differences make extrapolation from animals to humans unreliable.^{156,157} Given that most preclinical research in the use of nanocarrier-based therapeutics has been conducted on small rodent models of disease, concerns can be raised related to significant differences between these small animals and humans in terms of skin and bladder wall thickness (in research where nanocarriers are investigated as transdermal or intravesical delivery systems) and organ/body size (in research related

to externally placed magnets used in targeting paramagnetic nanoparticles). In addition, toxicity arising from changes in physicochemical properties of nanomaterials needs to be considered, even when the formulation of individual chemical components of the nanocarriers and therapeutic agents is considered to be safe.^{158,159}

Conclusion

In conclusion, despite a lag in the application of nanotechnology in non-oncologic compared with oncologic disease, there is a growing body of literature supporting its use in research and in novel therapeutics. As a delivery system, nanocarriers have several advantages over more conventional delivery systems, and in many ways, urogenital diseases are more amenable to its application than other diseases. Although there remain several obstacles and unknowns to clinical translation, many of these are being researched and overcome in other fields, and it is only a matter of time before there is widespread application of this technology to advance treatment of non-oncologic urogenital diseases.

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Not applicable.

Consent for publication
Not applicable.

Author contributions

Justin Loloi: Conceptualization; Investigation; Methodology; Writing – original draft; Writing – review & editing.

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Kelvin P. Davies: Conceptualization; Investigation; Methodology; Supervision; Writing – original draft; Writing – review & editing.

Sylvia O. Suadicani: Conceptualization; Investigation; Methodology; Supervision; Writing – original draft; Writing – review & editing.

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Figure 1 is derived from images created by unknown authors under a creative commons non-commercial license.

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References

- National Nanotechnology Initiative. <https://www.nano.gov> (accessed 3 August 2021).
- Su S and Kang PM. Recent advances in nanocarrier-assisted therapeutics delivery systems. *Pharmaceutics* 2020; 12: 837.
- Mitchell MJ, Billingsley MM, Haley RM, *et al.* Engineering precision nanoparticles for drug delivery. *Nat Rev Drug Discov* 2021; 20: 101–124.
- Chariou PL, Ortega-Rivera OA and Steinmetz NF. Nanocarriers for the delivery of medical, veterinary, and agricultural active ingredients. *ACS Nano* 2020; 14: 2678–2701.
- Durán-Lobato M, López-Estévez AM, Cordeiro AS, *et al.* Nanotechnologies for the delivery of biologicals: historical perspective and current landscape. *Adv Drug Deliv Rev* 2021; 176: 113899.
- Gorzalanny C, Mess C, Schneider SW, *et al.* Skin barriers in dermal drug delivery: which barriers have to be overcome and how can we measure them? *Pharmaceutics* 2020; 12: 684.
- Dalghi MG, Montalbetti N, Carattino MD, *et al.* The urothelium: life in a liquid environment. *Physiol Rev* 2020; 100: 1621–1705.
- Hsu CC, Chuang YC and Chancellor MB. Intravesical drug delivery for dysfunctional bladder. *Int J Urol* 2013; 20: 552–562.
- Tiwari N, Osorio-Blanco ER, Sonzogni A, *et al.* Nanocarriers for skin applications: where do we stand? *Angew Chem Int Ed Engl* 2021; 61: e202107960.
- GuhaSarkar S and Banerjee R. Intravesical drug delivery: challenges, current status, opportunities and novel strategies. *J Control Release* 2010; 148: 147–159.
- He MH, Chen L, Zheng T, *et al.* Potential applications of nanotechnology in urological cancer. *Front Pharmacol* 2018; 9: 745.
- Rew KT and Heidelbaugh JJ. Erectile dysfunction. *Am Fam Physician* 2016; 94: 820–827.
- Yafi FA, Jenkins L, Albersen M, *et al.* Erectile dysfunction. *Nat Rev Dis Primers* 2016; 2: 16003.
- Guyen E. Lipid-based nanoparticles in the treatment of erectile dysfunction. *Int J Impot Res* 2020; 32: 578–586.
- Liu SZ, Feng DC, Liu ZH, *et al.* Development of nanotechnology in andrology. *Transl Androl Urol* 2020; 9: 702–708.
- Masuku NP, Unuofin JO and Lebelo SL. Advances in nanoparticle delivery system for erectile dysfunction: an updated review. *Sex Med* 2021; 9: 100420.
- Wang AY and Podlasek CA. Role of nanotechnology in erectile dysfunction treatment. *J Sex Med* 2017; 14: 36–43.
- Andersson KE. PDE5 inhibitors – pharmacology and clinical applications 20 years after sildenafil discovery. *Br J Pharmacol* 2018; 175: 2554–2565.
- Huang SA and Lie JD. Phosphodiesterase-5 (PDE5) inhibitors in the management of erectile dysfunction. *P T* 2013; 38: 407–419.
- Linet OI and Neff LL. Intracavernous prostaglandin E1 in erectile dysfunction. *Clin Investig* 1994; 72: 139–149.
- Hackett GI. Patient preferences in treatment of erectile dysfunction: the continuing importance of patient education. *Clin Cornerstone* 2005; 7: 57–65.
- Davies KP. Development and therapeutic applications of nitric oxide releasing materials to treat erectile dysfunction. *Future Sci OA* 2015; 1: FSO53.
- Han G, Tar M, Kuppam DS, *et al.* Nanoparticles as a novel delivery vehicle for therapeutics targeting erectile dysfunction. *J Sex Med* 2010; 7: 224–233.
- Cabrales P, Han G, Roche C, *et al.* Sustained release nitric oxide from long-lived circulating nanoparticles. *Free Radic Biol Med* 2010; 49: 530–538.

25. Chouake J, Schairer D, Kutner A, *et al.* Nitrosoglutathione generating nitric oxide nanoparticles as an improved strategy for combating *Pseudomonas aeruginosa*-infected wounds. *J Drugs Dermatol* 2012; 11: 1471–1477.
26. Friedman A and Friedman J. New biomaterials for the sustained release of nitric oxide: past, present and future. *Expert Opin Drug Deliv* 2009; 6: 1113–1122.
27. Friedman AJ, Han G, Navati MS, *et al.* Sustained release nitric oxide releasing nanoparticles: characterization of a novel delivery platform based on nitrite containing hydrogel/glass composites. *Nitric Oxide* 2008; 19: 12–20.
28. Han G, Friedman AJ and Friedman JM. Nitric oxide releasing nanoparticle synthesis and characterization. *Methods Mol Biol* 2011; 704: 187–195.
29. Nacharaju P, Tuckman-Vernon C, Maier KE, *et al.* A nanoparticle delivery vehicle for S-nitroso-N-acetyl cysteine: sustained vascular response. *Nitric Oxide* 2012; 27: 150–160.
30. Rosen J, Landriscina A and Friedman AJ. Principles and approaches for optimizing therapy with unique topical vehicles. *J Drugs Dermatol* 2014; 13: 1431–1435.
31. Sanchez DA, Schairer D, Tuckman-Vernon C, *et al.* Amphotericin B releasing nanoparticle topical treatment of *Candida* spp. *Nanomedicine* 2014; 10: 269–277.
32. Tar M, Draganski A, Friedman J, *et al.* 021 topically applied sildenafil-nanoparticles improve erectile function in an aging-rat model of erectile dysfunction. *J Sex Med* 2018; 15: S10–S11.
33. Tar M, Cabrales P, Navati M, *et al.* Topically applied NO-releasing nanoparticles can increase intracorporal pressure and elicit spontaneous erections in a rat model of radical prostatectomy. *J Sex Med* 2014; 11: 2903–2914.
34. Tar MT, Friedman JM, Draganski A, *et al.* Topically delivered nitric oxide acts synergistically with an orally administered PDE5 inhibitor in eliciting an erectile response in a rat model of radical prostatectomy. *Int J Impot Res.* Epub ahead of print 20 May 2021. DOI: 10.1038/s41443-021-00451-6.
35. Goldstein I, Payton TR and Schechter PJ. A double-blind, placebo-controlled, efficacy and safety study of topical gel formulation of 1% alprostadil (Topiglan) for the in-office treatment of erectile dysfunction. *Urology* 2001; 57: 301–305.
36. McVary KT, Polepalle S, Riggi S, *et al.* Topical prostaglandin E1 SEPA gel for the treatment of erectile dysfunction. *J Urol* 1999; 162: 726–730; discussion 730.
37. Schanz S, Hauck EW, Schmelz HU, *et al.* Topical treatment of erectile dysfunction with prostaglandin E ethyl ester. *J Dtsch Dermatol Ges* 2009; 7: 1055–1059.
38. Park HS, Yang SW, Choi SU, *et al.* In vitro skin penetration and pharmacodynamic evaluation of prostaglandin E1 ethyl ester, a vasoactive prodrug of prostaglandin E1, formulated into alcoholic hydrogels. *Pharmazie* 2006; 61: 933–937.
39. Shaaya AN, Kraus C, Bauman DH, *et al.* Pharmacokinetics and bioavailability of papaverine HCl after intravenous, intracorporeal and penis topical administration in beagle dogs. *Methods Find Exp Clin Pharmacol* 1992; 14: 373–378.
40. Ali MF, Salem HF, Abdelmohsen HF, *et al.* Preparation and clinical evaluation of nano-transferosomes for treatment of erectile dysfunction. *Drug Des Devel Ther* 2015; 9: 2431–2447.
41. Liu C, Lopez DS, Chen M, *et al.* Penile rehabilitation therapy following radical prostatectomy: a meta-analysis. *J Sex Med* 2017; 14: 1496–1503.
42. Tong Y, Tar M, Melman A, *et al.* The opiorphin gene (ProL1) and its homologues function in erectile physiology. *BJU Int* 2008; 102: 736–740.
43. Kanika ND, Tar M, Tong Y, *et al.* The mechanism of opiorphin-induced experimental priapism in rats involves activation of the polyamine synthetic pathway. *Am J Physiol Cell Physiol* 2009; 297: C916–C927.
44. Podlasek CA, Meroz CL, Tang Y, *et al.* Regulation of cavernous nerve injury-induced apoptosis by sonic hedgehog. *Biol Reprod* 2007; 76: 19–28.
45. Dehsorkhi A, Castelletto V and Hamley IW. Self-assembling amphiphilic peptides. *J Pept Sci* 2014; 20: 453–467.
46. Hamley IW. Lipopeptides: from self-assembly to bioactivity. *Chemical Communications* 2015; 51: 8574–8583.
47. Yu YC, Pakalns T, Dori Y, *et al.* Construction of biologically active protein molecular architecture using self-assembling peptide-amphiphiles. *Methods Enzymol* 1997; 289: 571–587.
48. Angeloni NL, Bond CW, Tang Y, *et al.* Regeneration of the cavernous nerve by Sonic

- hedgehog using aligned peptide amphiphile nanofibers. *Biomaterials* 2011; 32: 1091–1101.
49. Choe S, Bond CW, Harrington DA, *et al.* Peptide amphiphile nanofiber hydrogel delivery of sonic hedgehog protein to the cavernous nerve to promote regeneration and prevent erectile dysfunction. *Nanomedicine* 2017; 13: 95–101.
 50. Angeloni N, Bond CW, Harrington D, *et al.* Sonic hedgehog is neuroprotective in the cavernous nerve with crush injury. *J Sex Med* 2013; 10: 1240–1250.
 51. Choe S, Veliceasa D, Bond CW, *et al.* Sonic hedgehog delivery from self-assembled nanofiber hydrogels reduces the fibrotic response in models of erectile dysfunction. *Acta Biomater* 2016; 32: 89–99.
 52. Dobbs R, Choe S, Kalmanek E, *et al.* Peptide amphiphile delivery of sonic hedgehog protein promotes neurite formation in penile projecting neurons. *Nanomedicine* 2018; 14: 2087–2094.
 53. Burgers JK, Nelson RJ, Quinlan DM, *et al.* Nerve growth factor, nerve grafts and amniotic membrane grafts restore erectile function in rats. *J Urol* 1991; 146: 463–468.
 54. Kim IG, Piao S, Lee JY, *et al.* Effect of an adipose-derived stem cell and nerve growth factor-incorporated hydrogel on recovery of erectile function in a rat model of cavernous nerve injury. *Tissue Eng Part A* 2013; 19: 14–23.
 55. Lin H, Dhanani N, Tseng H, *et al.* Nanoparticle improved stem cell therapy for erectile dysfunction in a rat model of cavernous nerve injury. *J Urol* 2016; 195: 788–795.
 56. Wu H, Tang WH, Zhao LM, *et al.* Nanotechnology-assisted adipose-derived stem cell (ADSC) therapy for erectile dysfunction of cavernous nerve injury: in vivo cell tracking, optimized injection dosage, and functional evaluation. *Asian J Androl* 2018; 20: 442–447.
 57. Liao CH, Wu YN, Chen BH, *et al.* Neuroprotective effect of docosahexaenoic acid nanoemulsion on erectile function in a rat model of bilateral cavernous nerve injury. *Sci Rep* 2016; 6: 33040.
 58. Charafeddine RA, Makdisi J, Schairer D, *et al.* Fidgetin-Like 2: a microtubule-based regulator of wound healing. *J Invest Dermatol* 2015; 135: 2309–2318.
 59. Baker L, Tar M, Kramer AH, *et al.* Fidgetin-like 2 negatively regulates axonal growth and can be targeted to promote functional nerve regeneration. *JCI Insight* 2021; 6: e138484.
 60. van der Wielen GJ, van Putten WL and Incrocci L. Sexual function after three-dimensional conformal radiotherapy for prostate cancer: results from a dose-escalation trial. *Int J Radiat Oncol Biol Phys* 2007; 68: 479–484.
 61. Jackson IL, Pavlovic R, Alexander AA, *et al.* BIO 300, a nanosuspension of genistein, mitigates radiation-induced erectile dysfunction and sensitizes human prostate cancer xenografts to radiation therapy. *Int J Radiat Oncol Biol Phys* 2019; 105: 400–409.
 62. Araña Rosáinz J, Ojeda MO, Acosta JR, *et al.* Imbalanced low-grade inflammation and endothelial activation in patients with type 2 diabetes mellitus and erectile dysfunction. *J Sex Med* 2011; 8: 2017–2030.
 63. Abdel Aziz MT, El Asmer MF, Rezaq A, *et al.* Novel water-soluble curcumin derivative mediating erectile signaling. *J Sex Med* 2010; 7: 2714–2722.
 64. Abdel Aziz MT, Motawi T, Rezaq A, *et al.* Effects of a water-soluble curcumin protein conjugate vs. *J Sex Med* 2012; 9: 1815–1833.
 65. Abdel Aziz MT, Rezaq AM, Atta HM, *et al.* Molecular signalling of a novel curcumin derivative versus Tadalafil in erectile dysfunction. *Andrologia* 2015; 47: 616–625.
 66. Zaahkhouk AM, Abdel Aziz MT, Rezaq AM, *et al.* Efficacy of a novel water-soluble curcumin derivative versus sildenafil citrate in mediating erectile function. *Int J Impot Res* 2015; 27: 9–15.
 67. Draganski A, Tar MT, Villegas G, *et al.* Topically applied curcumin-loaded nanoparticles treat erectile dysfunction in a rat model of type-2 diabetes. *J Sex Med* 2018; 15: 645–653.
 68. Tyagi P, Wu PC, Chancellor M, *et al.* Recent advances in intravesical drug/gene delivery. *Mol Pharm* 2006; 3: 369–379.
 69. Abrams P, Cardozo L, Fall M, *et al.* The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *Neurourol Urodyn* 2002; 21: 167–178.
 70. Milsom I, Stewart W and Thüroff J. The prevalence of overactive bladder. *Am J Manag Care*. 2000; 6(11 Suppl.):S565–S573.
 71. Reynolds WS, McPheeters M, Blume J, *et al.* Comparative effectiveness of anticholinergic therapy for overactive bladder in women: a systematic review and meta-analysis. *Obstet Gynecol* 2015; 125: 1423–1432.
 72. Madersbacher H and Jilg G. Control of detrusor hyperreflexia by the intravesical instillation of oxybutynine hydrochloride. *Paraplegia* 1991; 29: 84–90.
 73. Schröder A, Albrecht U, Schnitker J, *et al.* Efficacy, safety, and tolerability of intravesically

- administered 0.1% oxybutynin hydrochloride solution in adult patients with neurogenic bladder: a randomized, prospective, controlled multi-center trial. *Neurourol Urodyn* 2016; 35: 582–588.
74. Lehtoranta K, Tainio H, Lukkari-Lax E, *et al.* Pharmacokinetics, efficacy, and safety of intravesical formulation of oxybutynin in patients with detrusor overactivity. *Scand J Urol Nephrol* 2002; 36: 18–24.
 75. Saito M, Watanabe T, Tabuchi F, *et al.* Urodynamic effects and safety of modified intravesical oxybutynin chloride in patients with neurogenic detrusor overactivity: 3 years experience. *Int J Urol* 2004; 11: 592–596.
 76. Buyse G, Waldeck K, Verpoorten C, *et al.* Intravesical oxybutynin for neurogenic bladder dysfunction: less systemic side effects due to reduced first pass metabolism. *J Urol* 1998; 160: 892–896.
 77. Lazarus J. Intravesical oxybutynin in the pediatric neurogenic bladder. *Nat Rev Urol* 2009; 6: 671–674.
 78. Honda M, Kimura Y, Tsounapi P, *et al.* Long-term efficacy, safety, and tolerability of modified intravesical oxybutynin chloride for neurogenic bladder in children. *J Clin Med Res* 2019; 11: 256–260.
 79. Tyagi P, Kashyap M, Yoshimura N, *et al.* Past, present and future of chemodenervation with botulinum toxin in the treatment of overactive bladder. *J Urol* 2017; 197: 982–990.
 80. Nitti VW, Ginsberg D, Sievert KD, *et al.* Durable efficacy and safety of long-term OnabotulinumtoxinA treatment in patients with overactive bladder syndrome: final results of a 3.5-year study. *J Urol* 2016; 196: 791–800.
 81. Osborn DJ, Kaufman MR, Mock S, *et al.* Urinary retention rates after intravesical onabotulinumtoxinA injection for idiopathic overactive bladder in clinical practice and predictors of this outcome. *Neurourol Urodyn* 2015; 34: 675–678.
 82. Chuang YC, Tyagi P, Huang CC, *et al.* Urodynamic and immunohistochemical evaluation of intravesical botulinum toxin A delivery using liposomes. *J Urol* 2009; 182: 786–792.
 83. Kuo HC, Liu HT, Chuang YC, *et al.* Pilot study of liposome-encapsulated onabotulinumtoxinA for patients with overactive bladder: a single-center study. *Eur Urol* 2014; 65: 1117–1124.
 84. Chuang YC, Kaufmann JH, Chancellor DD, *et al.* Bladder instillation of liposome encapsulated onabotulinumtoxinA improves overactive bladder symptoms: a prospective, multicenter, double-blind, randomized trial. *J Urol* 2014; 192: 1743–1749.
 85. Byrne DS, Das A, Sedor J, *et al.* Effect of intravesical capsaicin and vehicle on bladder integrity control and spinal cord injured rats. *J Urol* 1998; 159: 1074–1078.
 86. Tyagi P, Chancellor MB, Li Z, *et al.* Urodynamic and immunohistochemical evaluation of intravesical capsaicin delivery using thermosensitive hydrogel and liposomes. *J Urol* 2004; 171: 483–489.
 87. Schnegelsberg B, Sun TT, Cain G, *et al.* Overexpression of NGF in mouse urothelium leads to neuronal hyperinnervation, pelvic sensitivity, and changes in urinary bladder function. *Am J Physiol Regul Integr Comp Physiol* 2010; 298: R534–R547.
 88. Evans RJ, Moldwin RM, Cossons N, *et al.* Proof of concept trial of tanezumab for the treatment of symptoms associated with interstitial cystitis. *J Urol* 2011; 185: 1716–1721.
 89. Kashyap M, Kawamorita N, Tyagi V, *et al.* Down-regulation of nerve growth factor expression in the bladder by antisense oligonucleotides as new treatment for overactive bladder. *J Urol* 2013; 190: 757–764.
 90. Portocarrero ML, Portocarrero ML, Sobral MM, *et al.* Prevalence of enuresis and daytime urinary incontinence in children and adolescents with sickle cell disease. *J Urol* 2012; 187: 1037–1040.
 91. Karakus S, Anele UA, Silva FH, *et al.* Urinary dysfunction in transgenic sickle cell mice: model of idiopathic overactive bladder syndrome. *Am J Physiol Renal Physiol* 2019; 317: F540–F546.
 92. Musicki B, Anele UA, Campbell JD, *et al.* Dysregulated NO/PDE5 signaling in the sickle cell mouse lower urinary tract: reversal by oral nitrate therapy. *Life Sci* 2019; 238: 116922.
 93. Karakus S, Musicki B, Navati MS, *et al.* NO-Releasing nanoparticles ameliorate detrusor overactivity in transgenic sickle cell mice via restored NO/ROCK signaling. *J Pharmacol Exp Ther* 2020; 373: 214–219.
 94. Raut P, Gambhire M, Panchal D, *et al.* Development and optimization of mirabegron solid lipid nanoparticles as an oral drug delivery for overactive bladder. *Pharm Nanotechnol* 2021; 9: 120–129.
 95. Hanno P and Dmochowski R. Status of international consensus on interstitial cystitis/bladder pain syndrome/painful bladder syndrome: 2008 snapshot. *Neurourol Urodyn* 2009; 28: 274–286.

96. Berry SH, Elliott MN, Suttorp M, *et al.* Prevalence of symptoms of bladder pain syndrome/interstitial cystitis among adult females in the United States. *J Urol* 2011; 186: 540–544.
97. Suskind AM, Berry SH, Ewing BA, *et al.* The prevalence and overlap of interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome in men: results of the RAND Interstitial Cystitis Epidemiology male study. *J Urol* 2013; 189: 141–145.
98. Ueda T, Hanno PM, Saito R, *et al.* Current understanding and future perspectives of interstitial cystitis/bladder pain syndrome. *Int Neurourol J* 2021; 25: 99–110.
99. Hanno PM, Erickson D, Moldwin R, *et al.* Diagnosis and treatment of interstitial cystitis/bladder pain syndrome: AUA guideline amendment. *J Urol* 2015; 193: 1545–1553.
100. Hanno PM, Burks DA, Clemens JQ, *et al.* AUA guideline for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome. *J Urol* 2011; 185: 2162–2170.
101. Garzon S, Laganà AS, Casarin J, *et al.* An update on treatment options for interstitial cystitis. *Prz Menopausalny* 2020; 19: 35–43.
102. Fraser MO, Chuang YC, Tyagi P, *et al.* Intravesical liposome administration—a novel treatment for hyperactive bladder in the rat. *Urology* 2003; 61: 656–663.
103. Parsons CL. The role of the urinary epithelium in the pathogenesis of interstitial cystitis/prostatitis/urethritis. *Urology* 2007; 69(4 Suppl.): 9–16.
104. Graham E and Chai TC. Dysfunction of bladder urothelium and bladder urothelial cells in interstitial cystitis. *Curr Urol Rep* 2006; 7: 440–446.
105. Tyagi P, Kashyap M, Majima T, *et al.* Intravesical liposome therapy for interstitial cystitis. *Int J Urol* 2017; 24: 262–271.
106. Chuang YC, Lee WC, Lee WC, *et al.* Intravesical liposome versus oral pentosan polysulfate for interstitial cystitis/painful bladder syndrome. *J Urol* 2009; 182: 1393–1400.
107. Peters KM, Hasenau D, Killinger KA, *et al.* Liposomal bladder instillations for IC/BPS: an open-label clinical evaluation. *Int Urol Nephrol* 2014; 46: 2291–2295.
108. Chen JL and Kuo HC. Clinical application of intravesical botulinum toxin type A for overactive bladder and interstitial cystitis. *Investig Clin Urol* 2020; 61(Suppl. 1): S33–S42.
109. Lee WC, Su CH, Tain YL, *et al.* Potential Orphan drug therapy of intravesical liposomal onabotulinumtoxin-a for ketamine-induced cystitis by mucosal protection and anti-inflammation in a rat model. *Sci Rep* 2018; 8: 5795.
110. Chuang YC and Kuo HC. A Prospective, multicenter, double-blind, randomized trial of bladder instillation of liposome formulation onabotulinumtoxin-a for interstitial cystitis/bladder pain syndrome. *J Urol* 2017; 198: 376–382.
111. Migita K and Eguchi K. FK 506-mediated T-cell apoptosis induction. *Transplant Proc* 2001; 33: 2292–2293.
112. Chuang YC, Tyagi P, Huang HY, *et al.* Intravesical immune suppression by liposomal tacrolimus in cyclophosphamide-induced inflammatory cystitis. *Neurourol Urodyn* 2011; 30: 421–427.
113. Nirmal J, Tyagi P, Chancellor MB, *et al.* Development of potential orphan drug therapy of intravesical liposomal tacrolimus for hemorrhagic cystitis due to increased local drug exposure. *J Urol* 2013; 189: 1553–1558.
114. Rajaganapathy BR, Janicki JJ, Levanovich P, *et al.* Intravesical liposomal tacrolimus protects against radiation cystitis induced by 3-beam targeted bladder radiation. *J Urol* 2015; 194: 578–584.
115. Liu HT, Tyagi P, Chancellor MB, *et al.* Urinary nerve growth factor level is increased in patients with interstitial cystitis/bladder pain syndrome and decreased in responders to treatment. *BJU Int* 2009; 104: 1476–1481.
116. Qu HC, Zhang W, Yan S, *et al.* Urinary nerve growth factor could be a biomarker for interstitial cystitis/painful bladder syndrome: a meta-analysis. *PLoS ONE* 2014; 9: e106321.
117. Tanner R, Chambers P, Khadra MH, *et al.* The production of nerve growth factor by human bladder smooth muscle cells in vivo and in vitro. *BJU Int* 2000; 85: 1115–1119.
118. Girard BM, Malley SE and Vizzard MA. Neurotrophin/receptor expression in urinary bladder of mice with overexpression of NGF in urothelium. *Am J Physiol Renal Physiol* 2011; 300: F345–F355.
119. Chen W, Ye DY, Han DJ, *et al.* Elevated level of nerve growth factor in the bladder pain syndrome/interstitial cystitis: a meta-analysis. *Springerplus* 2016; 5: 1072.
120. Kim SW, Im YJ, Choi HC, *et al.* Urinary nerve growth factor correlates with the severity of

- urgency and pain. *Int Urogynecol J* 2014; 25: 1561–1567.
121. Tonyali S, Ates D, Akbiyik F, *et al.* Urine nerve growth factor (NGF) level, bladder nerve staining and symptom/problem scores in patients with interstitial cystitis. *Adv Clin Exp Med* 2018; 27: 159–163.
 122. Yoshimura N, Oguchi T, Yokoyama H, *et al.* Bladder afferent hyperexcitability in bladder pain syndrome/interstitial cystitis. *Int J Urol* 2014; 21(Suppl. 1): 18–25.
 123. Majima T, Tyagi P, Dogishi K, *et al.* Effect of intravesical liposome-based nerve growth factor antisense therapy on bladder overactivity and nociception in a rat model of cystitis induced by hydrogen peroxide. *Hum Gene Ther* 2017; 28: 598–609.
 124. Warren JW. Catheter-associated bacteriuria in long-term care facilities. *Infect Control Hosp Epidemiol* 1994; 15: 557–562.
 125. Warren JW. Catheter-associated urinary tract infections. *Infect Dis Clin North Am* 1997; 11: 609–622.
 126. Lusardi G, Lipp A and Shaw C. Antibiotic prophylaxis for short-term catheter bladder drainage in adults. *Cochrane Database Syst Rev* 2013; 2013: Cd005428.
 127. Saint S. Clinical and economic consequences of nosocomial catheter-related bacteriuria. *Am J Infect Control* 2000; 28: 68–75.
 128. Trautner BW and Darouiche RO. Role of biofilm in catheter-associated urinary tract infection. *Am J Infect Control* 2004; 32: 177–183.
 129. Lebeaux D, Ghigo JM and Beloin C. Biofilm-related infections: bridging the gap between clinical management and fundamental aspects of recalcitrance toward antibiotics. *Microbiol Mol Biol Rev* 2014; 78: 510–543.
 130. Singha P, Locklin J and Handa H. A review of the recent advances in antimicrobial coatings for urinary catheters. *Acta Biomater* 2017; 50: 20–40.
 131. Bologna RA, Tu LM, Polansky M, *et al.* Hydrogel/silver ion-coated urinary catheter reduces nosocomial urinary tract infection rates in intensive care unit patients: a multicenter study. *Urology* 1999; 54: 982–987.
 132. Desai DG, Liao KS, Cevallos ME, *et al.* Silver or nitrofurazone impregnation of urinary catheters has a minimal effect on uropathogen adherence. *J Urol* 2010; 184: 2565–2571.
 133. Kilonzo M, Vale L, Pickard R, *et al.* Cost effectiveness of antimicrobial catheters for adults requiring short-term catheterisation in hospital. *Eur Urol* 2014; 66: 615–618.
 134. Kowalczyk D, Ginalska G, Piersiak T, *et al.* Prevention of biofilm formation on urinary catheters: comparison of the sparfloracin-treated long-term antimicrobial catheters with silver-coated ones. *J Biomed Mater Res B Appl Biomater* 2012; 100: 1874–1882.
 135. Lam TB, Omar MI, Fisher E, *et al.* Types of indwelling urethral catheters for short-term catheterisation in hospitalised adults. *Cochrane Database Syst Rev* 2014: Cd004013.
 136. Ogilvie AT, Brisson BA, Gow WR, *et al.* Effects of the use of silver-coated urinary catheters on the incidence of catheter-associated bacteriuria and urinary tract infection in dogs. *J Am Vet Med Assoc* 2018; 253: 1289–1293.
 137. Flores-Mireles AL, Pinkner JS, Caparon MG, *et al.* EbpA vaccine antibodies block binding of *Enterococcus faecalis* to fibrinogen to prevent catheter-associated bladder infection in mice. *Sci Transl Med* 2014; 6: 254ra127.
 138. Flores-Mireles AL, Walker JN, Bauman TM, *et al.* Fibrinogen release and deposition on urinary catheters placed during urological procedures. *J Urol* 2016; 196: 416–421.
 139. Guiton PS, Hannan TJ, Ford B, *et al.* *Enterococcus faecalis* overcomes foreign body-mediated inflammation to establish urinary tract infections. *Infect Immun* 2013; 81: 329–339.
 140. Alshehri SM, Aldalbahi A, Al-Hajji AB, *et al.* Development of carboxymethyl cellulose-based hydrogel and nanosilver composite as antimicrobial agents for UTI pathogens. *Carbohydr Polym* 2016; 138: 229–236.
 141. Roe D, Karandikar B, Bonn-Savage N, *et al.* Antimicrobial surface functionalization of plastic catheters by silver nanoparticles. *J Antimicrob Chemother* 2008; 61: 869–876.
 142. Dizaj SM, Lotfipour F, Barzegar-Jalali M, *et al.* Antimicrobial activity of the metals and metal oxide nanoparticles. *Mater Sci Eng C Mater Biol Appl* 2014; 44: 278–284.
 143. Rtimi S, Sanjines R, Pulgarin C, *et al.* Quasi-Instantaneous bacterial inactivation on Cu-Ag nanoparticulate 3D catheters in the dark and under light: mechanism and dynamics. *ACS Appl Mater Interfaces* 2016; 8: 47–55.
 144. Shalom Y, Perelshtein I, Perkas N, *et al.* Catheters coated with Zn-doped CuO nanoparticles delay the onset of catheter-associated urinary tract infections. *Nano Research* 2017; 10: 520–533.

145. Smith SD, Wheeler MA and Weiss RM. Nitric oxide synthase: an endogenous source of elevated nitrite in infected urine. *Kidney Int* 1994; 45: 586–591.
146. Wheeler MA, Smith SD, García-Cardena G, *et al.* Bacterial infection induces nitric oxide synthase in human neutrophils. *J Clin Invest* 1997; 99: 110–116.
147. Ahmadi MS, Lee HH, Sanchez DA, *et al.* Sustained nitric oxide-releasing nanoparticles induce cell death in candida Albicans yeast and hyphal cells, preventing biofilm formation in vitro and in a rodent central venous catheter model. *Antimicrob Agents Chemother* 2016; 60: 2185–2194.
148. Mihi MR, Cabral V, Patabhi R, *et al.* Sustained nitric oxide-releasing nanoparticles interfere with methicillin-resistant staphylococcus aureus adhesion and biofilm formation in a rat central venous catheter model. *Antimicrob Agents Chemother* 2017; 61: e02020.
149. Martinez LR, Mihi MR, Han G, *et al.* The use of chitosan to damage *Cryptococcus neoformans* biofilms. *Biomaterials* 2010; 31: 669–679.
150. Martinez LR, Mihi MR, Tar M, *et al.* Demonstration of antibiofilm and antifungal efficacy of chitosan against candidal biofilms, using an in vivo central venous catheter model. *J Infect Dis* 2010; 201: 1436–1440.
151. Al-Trad B, Aljabali A, Al Zoubi M, *et al.* Effect of gold nanoparticles treatment on the testosterone-induced benign prostatic hyperplasia in rats. *Int J Nanomedicine* 2019; 14: 3145–3154.
152. Koochi Hosseinabadi O, Behnam MA, Khoradmehr A, *et al.* Benign prostatic hyperplasia treatment using plasmonic nanoparticles irradiated by laser in a rat model. *Biomed Pharmacother* 2020; 127: 110118.
153. GuhaSarkar S, More P and Banerjee R. Urothelium-adherent, ion-triggered liposome-in-gel system as a platform for intravesical drug delivery. *J Control Release* 2017; 245: 147–156.
154. Liang C, Ortiz D, Ao-ieong E, *et al.* Localized increase of tissue oxygen tension by magnetic targeted drug delivery. *Nanotechnology* 2014; 25: 265102.
155. Toussaint M, Planché C, Duboc D, *et al.* Left ventricular ultrastructure in pulmonary stenosis and in tetralogy of Fallot. *Virchows Arch A Pathol Anat Histopathol* 1987; 411: 33–38.
156. Pound P and Ritskes-Hoitinga M. Is it possible to overcome issues of external validity in preclinical animal research? Why most animal models are bound to fail. *J Transl Med* 2018; 16: 304.
157. Robinson NB, Krieger K, Khan FM, *et al.* The current state of animal models in research: a review. *Int J Surg* 2019; 72: 9–13.
158. Najahi-Missaoui W, Arnold RD and Cummings BS. Safe nanoparticles: are we there yet? *Int J Mol Sci* 2020; 22: 385.
159. Sharma A, Madhunapantula SV and Robertson GP. Toxicological considerations when creating nanoparticle-based drugs and drug delivery systems. *Expert Opin Drug Metab Toxicol* 2012; 8: 47–69.

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