DRUG DELIVERY SYSTEMS AND METHODS FOR TREATMENT OF PROSTATE

Cross-Reference to Related Applications

This application claims the benefit of U.S. Provisional Patent Application No. 61/696,029, filed August 31, 2012, which is incorporated herein by reference.

Background

Delivery of diagnostic or therapeutic agents to the prostate is difficult. Current practice requires systemic administration, such as by intravenous, intramuscular, oral, transdermal, or intranasal routes, using doses which result in significant exposure to healthy tissues and relatively low exposure within the prostate gland. Frequently the systemic exposure leads to unwanted or harmful side effects which limit the usefulness of the therapeutic agent in treating prostate disease.

Targeted and local delivery strategies have been explored to minimize peripheral exposure with limited success. Some targeting strategies rely on prostate cells to express specific receptors to which a drug-targeting ligand complex binds. These receptors may not always be present, limiting the utility of the approach. The receptor density on prostate cells also can vary widely and restrict the actual amount of drug delivered to the prostate. In addition, other cells in the body may also express the same receptor leading to unwanted drug exposure. Lastly, the drug targeting ligand complex can be degraded prior to reaching the prostate, defeating the targeting mechanism.

Direct injection into or near the prostate also has been tried. Patient acceptance is low due to the pain and risk of infection. In addition, the mean residence time of the drug often is relatively short, which necessitates the use of multiple injections for treatment. Furthermore, the disruption of prostate tumors during injection can lead to metastasis. Depot formulations extend the drug presence in the prostate but reduce the amount of drug that can be injected into the prostate and may enhance local tissue toxicity.

Radionucleotide-containing pellets placed near the prostate are used to treat prostate cancer but provide only one treatment modality. Radiation therapy is also non-selective, leading to significant damage to surrounding healthy tissue structures including nerves.

The use of a suppository or drug eluting stent placed in the prostatic urethra is known, but these are difficult to place and poorly tolerated in men. Furthermore, these delivery means have a limited payload capacity.

Accordingly, there remains a need for improved drug delivery methods and systems for treating the prostate, such as in the treatment of prostate cancer or prostatitis.

Summary

In one aspect, the present invention refers to use of gemcitabine in the manufacture of a medicament for the treatment of prostate cancer, wherein the medicament is to be locally administered into the bladder of a patient to achieve a sustained concentration of the medicament in the urine in the bladder sufficient to produce a therapeutic concentration of the medicament in the prostate, wherein the medicament is to be locally administered into the patient's bladder at a mean average amount of from 1 mg/day to 300 mg/day of the gemcitabine, and wherein the medicament is to be locally administered into the patient's bladder continuously over a period of over 6 hours. In one example, a medicament is disclosed that includes gemcitabine for use in the treatment of the prostate by locally administering the gemcitabine into the bladder of a patient to achieve a sustained concentration of the drug in the urine in the bladder sufficient to produce a therapeutic concentration of the drug in the prostate, wherein the locally administering into the patient's bladder is at a mean average amount of from 1 mg to about 300 mg per day. The locally administering of gemcitabine may be continuous or intermittent. In one example, the patient is in need of treatment for prostate cancer. In an example, the gemcitabine is delivered into the bladder from an intravesical drug delivery device which continuously releases the gemcitabine into the urine in the bladder over a sustained period. In an alternative example, the gemcitabine is delivered into the bladder from a coating substance applied to the bladder, which coating substance continuously releases the gemcitabine into the urine in the bladder over a sustained period. The coating substance may include a mucoadhesive formulation. In a further alternative example, a liquid form of the gemcitabine is pumped into the bladder through a urethral catheter inserted into the bladder. In various examples, the gemcitabine is released into the patient's bladder continuously over a period of at least 2 hours, such as from 1 day to 14 days. In an example, the gemcitabine is released into the patient's bladder at a mean average amount of from 1 mg to about 100 mg gemcitabine per day for up to 7 days. In another example, the gemcitabine is released into the patient's bladder at a mean average amount of from 20 mg to 300 mg per day for up to 7 days. In another aspect, the present invention refers to a drug delivery device comprising a

medicament as disclosed herein, configured to locally administer the gemcitabine into the bladder continuously over a period of at least 6 hours, when the drug delivery device is to be inserted into the bladder, wherein the device is configured to release the gemcitabine into the bladder in an amount therapeutically effective for the treatment of prostate cancer, wherein the device is configured to release gemcitabine into the bladder at a mean average amount of from 1 mg/day to 300 mg/day of the gemcitabine. In one example, there is disclosed a drug delivery device comprising a medicament as disclosed herein, configured to locally administer the gemcitabine into the bladder continuously over a period of at least 6 hours, when the drug delivery device is to be inserted into the bladder. In another example, there is disclosed a drug delivery device comprising a medicament as disclosed herein, configured to release the gemcitabine when the drug delivery device is inserted into the bladder. In a further aspect, the present invention refers to a medical device comprising: a housing configured for intravesical insertion; and a dosage form comprising gemcitabine, wherein the housing holds the dosage form and is configured to release the gemcitabine into the bladder in an amount therapeutically effective for the treatment of prostate cancer, wherein the device is configured to release gemcitabine into the bladder at a mean average amount of from 1 mg/day to 300 mg/day of the gemcitabine, and wherein the device is configured to release gemcitabine into the bladder continuously over a period of over 6 hours. In another example, a medical device is disclosed for intravesical administration of gemcitabine. In an example, the medical device includes a housing configured for intravesical insertion and a dosage form including gemcitabine, wherein the housing holds the dosage form and is configured to release the gemcitabine into the bladder in an amount therapeutically effective for the treatment of the prostate, and wherein the device is configured to

release gemcitabine into the bladder at a mean average amount of from 1 mg to about 300 mg per day of the gemcitabine. The gemcitabine contained in the housing may be in a non-liquid form. The housing may be elastically deformable between a retention shape configured to retain the device in a patient's bladder and a deployment shape for passage of the device through the patient's urethra. In an example, the device is configured to release from 1 mg to 100 mg of gemcitabine per day for up to 7 days. In another example, the device is configured to release from 20 mg to 300 mg of gemcitabine per day for up to 7 days.

In yet another aspect, the present invention refers to use of gemcitabine in the manufacture of a medicament for treatment of prostate cancer in a patient in need thereof, wherein the medicament is to be locally administered into the bladder of the patient to achieve a sustained concentration of the gemcitabine in urine in the bladder sufficient to produce a therapeutic concentration of the gemcitabine in the prostate, and wherein the medicament is to be locally administered into the bladder continuously over a period of over 6 hours. In still another example, a method is provided of administering a drug to a patient in need of treatment of the prostate. The method includes locally administering gemcitabine into the bladder of a patient to achieve a sustained concentration of the gemcitabine in urine in the bladder sufficient to produce a therapeutic concentration of the gemcitabine in the prostate. In one example, the method includes administering at least a second therapeutic agent to the patient. The second therapeutic agent may be administered intravesically. The second therapeutic agent may include a cytotoxic agent, an analgesic agent, an anti-inflammatory agent, or a combination thereof. The second therapeutic agent may prevent, treat, or ameliorate cystitis of the bladder.

In one example, there is provided the use of gemcitabine in the manufacture of a medicament for the treatment of prostate cancer, wherein the medicament is to be locally administered into the bladder of a patient to achieve a sustained concentration of the medicament in the urine in the bladder sufficient to produce a therapeutic concentration of the medicament in the prostate, wherein the medicament is to be locally administered into the patient's bladder at a mean average amount of from 1 mg/day to 300 mg/day of the gemcitabine.

In one example, there is provided the use of gemcitabine in the manufacture of a medicament for treatment of prostate cancer in a patient in need thereof, wherein the medicament is to be locally administered into the bladder of the patient to achieve a sustained concentration of the gemcitabine in urine in the bladder sufficient to produce a therapeutic concentration of the gemcitabine in the prostate.

Brief Description of the Drawings

FIGS. 1A-1B illustrate one embodiment of an intravesical drug delivery device that may be used for administering gemcitabine as described herein.

FIGS. 2A-2B illustrate another embodiment of an intravesical drug delivery device that may be used for administering gemcitabine as described herein.

FIGS. 3A-3C illustrate still another embodiment of an intravesical drug delivery device that may be used for administering gemcitabine as described herein.

FIGS. 4A-4B illustrate a method of inserting an intravesical drug delivery device into the bladder of a patient for local administration of gemcitabine as described herein.

FIG. 5A illustrates a material applied to the inner surface of the bladder wall for local administration of gemcitabine as described herein.

FIG. 5B illustrates a method of applying a coating material onto to the inner surface of the bladder wall for local administration of gemcitabine as described herein.

FIG. 6 illustrates a method of applying a liquid drug or drug formulation into the bladder.

FIG. 7 illustrates the concentration of gemcitabine in the prostate after bladder perfusion and intravenous administration.

FIG. 8 illustrates the plasma levels of gemcitabine after bladder perfusion and intravenous administration.

FIG. 9 illustrates ^{14}C gemcitabine concentration in the bladder after bladder perfusion and intravenous administration.

FIG. 10 illustrates oxaliplatin terminal concentrations after bladder perfusion.

FIG. 11 illustrates cisplatin terminal concentrations after bladder perfusion and intravenous administration.

Detailed Description

It has been discovered that intravesical administration can be used to deliver a therapeutically effective amount of gemcitabine to a patient's prostate over a short or extended period while minimizing systemic exposure of the drug. For example, a controlled amount of drug may be dissolved in urine in the patient's bladder in a concentration and over a time sufficient to produce therapeutic concentrations of the drug in the prostate. Because the bladder limits the absorption of urine components into the general circulation, systemic exposure to the drug is advantageously minimized.

A variety of methods can be used to achieve the required urine concentrations of the gemcitabine. In one embodiment, the drug can be provided by direct instillation of a simple solution into the bladder. For example, a solution of the drug may be pumped into the bladder through a urethral or suprapubic catheter in a continuous or pulsatile manner over the treatment period. In another embodiment, the drug is released from a device or composition deployed in the bladder, wherein the device or composition releases the drug (continuously or intermittently) at a rate effective to produce the desired concentration of drug in the urine over a specified treatment period. For example, the drug may be released from an intravesically-inserted device into the bladder and then the drug diffuses from the bladder to the prostate. At the end of the treatment period, the device may be retrieved from the bladder, or it may be eliminated by being resorbed, dissolved, excreted, or a combination thereof.

In a preferred embodiment, the drug is gemcitabine, which is effective in treating prostate cancer. The therapeutic utility of gemcitabine to treat prostate diseases is thought to be the result

of the unique combination of the compound's physical and chemical properties which facilitate prostate uptake following intravesical administration and high intrinsic drug potency toward prostate tumor cells. See Examples below.

In other embodiments, the drug may be essentially any suitable drug, including but not limited to ones useful in the treatment of prostate cancer, benign prostatic hyperplasia, or prostatitis. For example, the drug may be an antibiotic, an alpha blocker, an anti-inflammatory, an alpha 1A antiadrenergic, an antiandrogen, a microtubule inhibitor, or a 5 alpha reductase inhibitor. Examples of other drugs include but are not limited to ciproflaxin, trimethoprim, docetaxel, and finasteride.

In a preferred embodiment, the drug is administered to the prostate from an intravesical device. Preferred examples of intravesical drug delivery devices and methods of deploying those devices into the bladder are described in the following U.S. Patent Application Publications: US 2012/0203203 (Lee et al.); US 2012/0089122 (Lee et al.); US 2012/0089121 (Lee et al.); US 2011/0218488 (Boyko et al.); US 2011/0202036 (Boyko et al.); US 2011/0152839 (Cima et al.); US 2011/0060309 (Lee et al.); US 2010/0331770 (Lee et al.); US 2010/0330149 (Daniel et al.); US 2010/0003297 (Tobias et al.); US 2009/0149833 (Cima et al.); and US 2007/0202151 (Lee et al.).

In embodiments in which the drug is delivered from an intravesical drug delivery device, the drug may be housed in the device in various forms, which may depend on the particular mechanism by which the device controllably releases the drug into fluid (e.g., urine) in the bladder. In some embodiments, the drug is provided in a solid, semi-solid, or other non-liquid form, which advantageously may facilitate stable storage of the drug before the device is used and advantageously may enable the drug payload of the device to be stored in smaller volume than would be possible if the drug were housed in the form of a liquid solution. In an embodiment the non-liquid form is selected from tablets, granules, semisolids, capsules, and combinations thereof. In one embodiment, the drug is in the form of a plurality of tablets, such as mini-tablets described in U.S. Patent No. 8,343,516. In other embodiments, the drug may be housed in a liquid form, such as in a solution with a pharmaceutically acceptable excipient.

An embodiment of a drug delivery device **100** is illustrated in **FIG. 1A**. The device **100** includes a device body having a drug reservoir portion **102** and a retention frame portion **104**. In **FIG. 1**, the device **100** is shown in a relatively expanded shape suited for retention in the body.

Following deployment into the body, the device **100** may assume the relatively expanded shape to retain the drug delivery device in the body cavity or lumen.

For the purposes of this disclosure, terms such as "relatively expanded shape", "relatively higher-profile shape", or "retention shape" generally denote any shape suited for retaining the device in the intended implantation location, including but not limited to the pretzel shape shown in **FIG. 1** that is suited for retaining the device in the bladder. Similarly, terms such as "relatively lower-profile shape" or "deployment shape" generally denote any shape suited for deploying the drug delivery device into the body, including a linear or elongated shape that is suited for deploying the device through the working channel of catheter, cystoscope, or other deployment instrument positioned in the urethra. In embodiments, the drug delivery device may naturally assume the relatively expanded shape and may be deformed, either manually or with the aid of an external apparatus, into the relatively lower-profile shape for insertion into the body. Once deployed the device may spontaneously or naturally return to the initial, relatively expanded shape for retention in the body.

In the illustrated embodiment, the drug reservoir and retention frame portions **102, 104** of the drug delivery device **100** are longitudinally aligned and are coupled to each other along their length, although other configurations are possible. The drug delivery device **100** includes an elastic or flexible device body **106** that defines a drug reservoir lumen **108** (i.e., the drug housing) and a retention frame lumen **110**. The drug reservoir lumen **108** is designed to house a drug formulation that comprises the drug. In the illustrated embodiment, the drug formulation in the form of a number of solid drug tablets **112**. The retention frame lumen **110** is designed to house a retention frame **114** to form the retention frame portion **104**. The illustrated lumens **108, 110** are discrete from each other, although other configurations are possible.

As shown in the cross-sectional view of **FIG. 1B**, the device body **106** includes a tube or wall **122** that defines the drug reservoir lumen **108** and a tube or wall **124** that defines the retention frame lumen **110**. The tubes **122, 124** and lumens **108, 110** can be substantially cylindrical, with the drug reservoir lumen **108** having a relatively larger diameter than the retention frame lumen **110**, although other configurations can be selected based on, for example, the amount of drug to be delivered, the diameter of the retention frame, and deployment considerations such as the inner diameter of the deployment instrument. The wall **124** that defines the retention frame lumen **110** may extend along the entire length of the wall **122** that

defines the drug reservoir lumen **108**, so that the retention frame lumen **110** has the same length as the drug reservoir lumen **108** as shown, although one wall may be shorter than the other wall in other embodiments. The two walls **122, 124** are attached along the entire length of the device in the illustrated embodiment, although intermittent attachment can be employed.

As shown in **FIG. 1A**, the drug reservoir lumen **108** is loaded with a number of drug units **112** in a serial arrangement. Essentially any number of drug units may be used, for example, depending upon the sizes of the reservoir and the drug units. The drug reservoir lumen **108** includes a first end opening **130** and an opposed second end opening **132**. Once the drug units **112** are loaded, restraining plugs **120** are disposed in the openings **130** and **132**. The restraining plugs **120**, in this embodiment, are cylindrical plugs secured into the entry **130** and the exit **132**. In other embodiments, the openings **130** and **132** are closed off with other structures or materials, which may, depending on the particular embodiments, include an aperture or a water- or drug-permeable wall to facilitate ingress or egress of water or drug during use.

The retention frame lumen **110** is loaded with the retention frame **114,** which may be an elastic wire. The retention frame **110** may be configured to return spontaneously to a retention shape, such as the illustrated example "pretzel" shape or another coiled shape, such as those disclosed in the applications previously incorporated. In particular, the retention frame **114** may retain the device **100** in the body, such as in the bladder. For example, the retention frame **114** may have an elastic limit and modulus that allows the device **100** to be introduced into the body in a relatively lower-profile shape, permits the device **100** to return to the relatively expanded shape once inside the body, and impedes the device from assuming the relatively lower-profile shape within the body in response to expected forces, such as the hydrodynamic forces associated with contraction of the detrusor muscle and urination. Thus, the device **100** may be retained in the body once implanted, limiting or prevent accidental expulsion.

The material used to form the device body **106**, at least in part, may be elastic or flexible to permit moving the device **100** between deployment and retention shapes. When the device is in the retention shape, the retention frame portion **104** may tend to lie inside the drug reservoir portion **102** as shown, although the retention frame portion **104** can be positioned inside, outside, above, or below the drug reservoir portion **102** in other cases.

The material used to form the device body **106** may be water permeable so that solubilizing fluid (*e.g.*, urine or other bodily fluid) can enter the drug reservoir portion **102** to solubilize the drug units **112** once the device is implanted. For example, silicone or another biocompatible elastomeric material may be used. In other embodiments, the device body may be formed, at least in part, of a water-impermeable material.

FIG. 2A illustrates an implantable drug delivery device **200**, which includes a drug reservoir **202** loaded with drug **212** and a retention structure that includes two filaments **220**, **222** associated with a fastener **230**. As shown, the drug reservoir **202** is an elongated tube that can be deformed between a relatively linear deployment shape, such as the shape shown in **FIG. 2A**, and a relatively circular retention shape, such as the shape shown in **FIG. 2B.** The drug **212** may be loaded in the tube in a flexible form, so that the drug reservoir **102** can be moved between the two shapes. For example, the drug **212** may be a number of solid drug tablets, a liquid, or a gel. The filaments **220**, **222** may be attached to opposite ends of the drug reservoir **202** and joined by the fastener **230**. The fastener **230** can be adjusted to adjust the position of one filament **220** with reference to the other **222**, thereby adjusting the position of one end of the drug reservoir **202** with reference to the other end. The device **200** can assume the retention shape by adjusting the filaments **220**, **222** to draw the ends of the drug reservoir **202** closer together, and thereafter the device **200** can be retained in the retention shape by preventing adjustment of the filaments **220**, **222** with the fastener **230**. In such an embodiment, the device **200** is manually adjusted into the retention shape by manually adjusting the filaments **220**, **222** after the device **200** is inserted into the bladder.

In the illustrated embodiment, the fastener **230** is a cinch nut that permits shortening the portion of the filaments **220**, **222** between the drug reservoir ends and the cinch nut, but prevents lengthening of these portions of the filaments **220**, **222**. Thus, the ends of the drug reservoir **202** can be drawn closer together by pulling one or both of the filaments **220**, **222** through the cinch nut, causing the device **200** to assume the retention shape. Once the filaments **220**, **222** have been so adjusted, the cinch nut prevents lengthening of the filaments **220**, **222**, retaining the device in the retention shape. Thus, manually adjusting the device **200** into the retention shape once implanted merely requires pulling one or both of the filaments **220**, **222**, although other fasteners **230** that require separate manipulation can be employed. Other fasteners may also be used.

Another embodiment of an intravesical drug delivery device is illustrated in **FIGS. 3A-3C**. In this embodiment, the device includes a housing **300** having a single, continuous structure with multiple, discrete drug reservoir lumens **320** and optionally having at least one retention frame lumen **330** in which a retention frame **360** is disposed. Each drug reservoir lumen **320** has two defined openings, as shown in **FIG. 3B**, and is dimensioned to hold at least one solid drug unit **340**. Solid drug unit **340** may be a drug tablet or capsule. In other embodiments not shown, each drug reservoir lumen has one defined opening. The housing may be formed of a flexible polymer, such as silicone. **FIG. 3B** is a cross-sectional view of the plane that bisects one of the drug reservoir lumens **320** of the housing shown in **FIG. 3A** along line 3B-3B. As shown in **FIG. 3B**, the monolithic housing **300** has two defined openings (**350a**, **350b**) in its drug reservoir lumen **320** that expose both ends of the solid drug unit **340**. The retention frame lumen **330**, in this embodiment, is aligned parallel to the longitudinal axis of the housing and perpendicular to the drug reservoir lumen **320**. **FIG. 3C** is a perspective view of a portion of the embodiment of the device **300** shown in **FIG. 3A** when the device is in its retention shape, which is taken when the retention frame **360** is disposed in the retention frame lumen **330**. The drug reservoir lumens **320** and the retention frame **360** in the housing of this embodiment are oriented so that the drug reservoir lumens **320** are outside the retention frame's **360** arc. Alternatively, the housing in **FIG. 3C** can be rotated 180 degrees about the retention frame **360** to yield a configuration in which the drug reservoir lumens **320** are arranged within the retention frame's **360** arc. With this embodiment, the devices provide sufficient direct contact between solid drug units and with urine surrounding the device when deployed and retained in the bladder. In embodiments, release of the drug from the device is controlled by erosion of an exposed portion of the surface of a solid drug unit, such that the rate of drug release from the drug delivery device may be directly proportional to and limited by the total exposed surface area of the solid drug units.

One embodiment of inserting an intravesical device **400** for subsequent controlled release of the drug into the bladder is shown in **FIGS. 4A** and **4B**. Here, the device **400** is shown assuming a retention shape as the device exits a deployment instrument **402**. The deployment instrument **402** may be any suitable device. It may be a lumenal device, such as a catheter, urethral catheter, or cystoscope. The deployment instrument **402** may be a commercially available device or a device specially adapted for the present drug delivery devices. **FIG. 4B** illustrates the insertion of the device **400** into the bladder, wherein the adult male anatomy is

shown by way of example. The deployment instrument **402** is inserted through the urethra to the bladder, and the device **400** may be passed from/through the deployment instrument **402**, driven by a stylet or flow of lubricant or combination thereof until the device **400** exits into the bladder, and as shown is in a retention shape.

In various embodiments, the drug may be released from the intravesical drug delivery device by diffusion to through a wall of the drug housing, by diffusion to through one or more defined apertures in a wall of the drug housing, by osmotic pressure through an aperture in the drug housing, by erosion of a drug formulation in contact with urine in the bladder, or by a combination thereof.

In some embodiments in which the device comprises a drug in a solid form, elution of drug from the device occurs following dissolution of the drug within the device. Bodily fluid enters the device, contacts the drug and solubilizes the drug, and thereafter the dissolved drug diffuses from the device or flows from the device under osmotic pressure or via diffusion. For example, the drug may be solubilized upon contact with urine in cases in which the device is implanted in the bladder.

In various embodiments, the intravesical device may release the drug continuously or intermittent to achieve a concentration of the drug in the bladder that produces a sustained, therapeutically effective concentration of the drug in the prostate over a period from 1 hour to 1 month, for example from 2 hours to 2 weeks, from 6 hours to 1 week, from 24 hours to 72 hours, etc.

In various embodiments, the intravesical device may release the gemcitabine or other drug in an amount of from 1 mg/day to 100 mg/day, for example from 20 mg/day to 300 mg/day or from 25 mg/day to 300 mg/day.

In another embodiment, a coating substance may be intravesically applied to the bladder wall, wherein the coating substance includes the gemcitabine or other drug and one or more excipient materials that promote adherance of the coating substance to the bladder wall and provides continuous controlled release of the drug over the treatment period. The coating substance may be a mucoadhesive formulation, such as gels, ointments, creams, films, emulsion gels, tablets, polymers, or a combination thereof. Mucoadhesive formulation polymers may include hydrogels or hydrophilic polymers, polycarbophil (i.e. Carbopols, etc.), chitosan, polyvinylpyrrolidone (PVP), lectin, polyethyleneglycolated polymers, celluloses, or a

combination thereof. Suitable celluloses include methyl cellulose (MC), carboxymethyl cellulose (CMC), hydroxypropyl cellulose (HPC), or combinations thereof. The coating substance may include a permeation enhancer. Non-limiting examples of permeation enhancers include dimethyl sulfoxide (DMSO), sodium carboxymethyl cellulose (NaCMC), lipids, surfactants, or combinations thereof. As shown in **FIG. 5A**, a coating substance **500** may be deployed in the bladder **550** so that the coating substance **500** engages the bladder wall **552**.

The coating substance may be deployed in the bladder using a deployment instrument. **FIG. 5B** is a sagittal view of a male genitourinary system, illustrating a coating substance **500** being deployed through a deployment instrument **502** into an implantation site. By way of example, the male anatomy is shown and the implantation site is shown as the bladder **550**. The coating substance **500** may be an embodiment of one of the coating substances described herein. The deployment instrument **502** may be any device designed to navigate natural lumens of the body to reach the intended implantation site. For deployment in the bladder **550**, the deployment instrument **502** is sized and shaped for passing through a urethra **560** of a patient to a bladder **550** as shown. The deployment instrument **502** may be a known device, such as a catheter or cystoscope, or a specially designed device. The deployment instrument **502** is used to deploy the coating substance **500** into the body and is subsequently removed from the body, leaving the coating substance **500** wholly implanted in the body. Once so implanted, the coating substance **500** may release drug into the body for an extended period. A comparable procedure can be used to deploy any of the devices or drugs described herein into other parts of the body through other natural lumens. For example, as shown in **FIG. 6**, a deployment instrument **602** can be used to deploy a liquid drug or drug formulation **600** into the bladder **650** by passing the deployment instrument **602** through a urethra **660**.

In one embodiment, a second therapeutic agent is administered to the patient. The second therapeutic agent may be administered intravesically. The methods and systems described herein may be used to administer the second therapeutic agent intravesically. The second therapeutic agent may include a cytotoxic agent, an analgesic agent, an anti-inflammatory agent, or a combination thereof. In one embodiment, the second therapeutic agent prevents, treats, or ameliorates cystitis of the bladder.

The intravesical methods and systems described herein also may be used to deliver therapeutic concentrations to bladder-regional tissues besides the prostate. For example,

maintaining a drug urine concentration at a certain level may achieve therapeutic concentrations of drug in the ureters, kidneys, urethra, lower portions of the peritoneum, regional lymph nodes, uterus, ovaries, distal portions of large bowel, including the rectum and pelvic floor musculature.

The term "patient" as used herein refers to humans or other mammals, such as in veterinary or livestock applications. In a particular embodiment, the patient is an adult human male.

The present invention may be further understood with reference to the following non-limiting examples.

Example 1: Gemcitabine Prostate Uptake from Bladder

A study was conducted on male Sprague Dawley rats administering ^{14}C gemcitabine by intra-urinary bladder cannula, over a 6- or 24-hour continuous perfusion, or by a single IV bolus. The 6- and 24-hour continuous perfusions perfused 6.9 and 26.6 mg, respectively, of gemcitabine into the bladder. The single IV bolus included 5.0 mg of gemcitabine.

Blood (**FIG. 8**), urine, and tissue samples (e.g., bladder, prostate)(**FIGS. 7** and **9**) were collected and analyzed for gemcitabine content. The results are illustrated in **FIGS. 7-9**. The results show that sustained gemcitabine urine concentrations have been found to produce significant gemcitabine levels in bladder tissue, which are at or exceed therapeutic concentrations based on *in vitro* bladder cancer cell experiments. The gemcitabine levels in the bladder are shown in **FIG. 9**, which also depicts a significantly lower concentration of gemcitabine in the bladder 24 hours after a clinically relevant IV dose.

Similar and unexpected results have been observed in prostate tissue, as shown in **FIG. 7**. In particular, prostate gemcitabine tissue concentrations are substantially higher than those observed after IV administration. Furthermore, the absolute tissue levels are well above the concentrations shown to kill prostate cancer cells *in vitro*, which range from 10 ng/mL to 200 ng/mL.

In contrast, it is noted that Phase 2 clinical studies of gemcitabine prostate cancer patients have shown limited efficacy. It is also noted that animal studies have shown liposomal formulations of gemcitabine dramatically enhance efficacy—which activity was thought to be the result of improved tumor exposure, because (i) liposomes may protect gemcitabine from rapid metabolism, and (ii) liposomes may improve gemcitabine prostate tissue concentrations. Accordingly, in view of the present animal study, which shows the unexpected accumulation of

gemcitabine in prostate tissue following administration of gemcitabine in urine, it is believed that intravesical delivery of gemcitabine will produce superior gemcitabine efficacy in prostate cancer without significant systemic exposure.

Example 2: Limited Prostate Uptake of Cisplatin and Oxaliplatin from Bladder

In a similar study to Example 1 oxaliplatin or cisplatin were administered to male Sprague Dawley rats by intra-urinary bladder cannula, over a 6- or 24-hour continuous perfusion, or by a single IV bolus. As shown in **FIG. 10** and **FIG. 11**, oxaliplatin and cisplatin prostate partitioning, although achieving therapeutic bladder concentrations and kidney concentrations following cisplatin, exhibit poor partitioning into the prostate.

Publications cited herein and the materials for which they are cited are specifically incorporated by reference. Modifications and variations of the methods and devices described herein will be obvious to those skilled in the art from the foregoing detailed description. Such modifications and variations are intended to come within the scope of the appended claims.

What is claimed is:

1. Use of gemcitabine in the manufacture of a medicament for the treatment of prostate cancer, wherein the medicament is to be locally administered into the bladder of a patient to achieve a sustained concentration of the medicament in the urine in the bladder sufficient to produce a therapeutic concentration of the medicament in the prostate,

   wherein the medicament is to be locally administered into the patient's bladder at a mean average amount of from 1 mg/day to 300 mg/day of the gemcitabine, and wherein the medicament is to be locally administered into the patient's bladder continuously over a period of over 6 hours.

2. The use of claim 1, wherein the medicament is to be administered into the bladder from an intravesical drug delivery device which continuously releases the medicament into the urine in the bladder over the period.

3. The use of claim 2, wherein the intravesical drug delivery device continuously releases the medicament into the urine in the bladder over a period of 1 day to 14 days.

4. The use of claim 2, wherein the intravesical drug delivery device comprises a housing which contains and controllably releases the medicament and is elastically deformable between a retention shape configured to retain the device in a patient's bladder and a deployment shape for passage of the device through the patient's urethra.

5. The use of claim 4, wherein the medicament contained in the housing is in a non-liquid form.

6. The use of claim 5, wherein the non-liquid form is selected from the group consisting of tablets, granules, semisolids, capsules, and combinations thereof.

7. The use of claim 1, wherein the medicament is to be delivered into the bladder from a coating substance applied to the bladder, which coating substance releases the medicament into the urine in the bladder over a sustained period.

8. The use of claim 7, wherein the coating substance comprises a mucoadhesive formulation.

9. The use of claim 1, wherein the locally administered comprises pumping a liquid form of the medicament into the bladder through a urethral catheter which is to be deployed into the bladder.

10. The use of any one of claims 1 to 9, wherein the medicament is to be locally administered into the patient's bladder from 1 mg/day to 100 mg/day of the gemcitabine for up to 7 days.

11. The use of any one of claims 1 to 9, wherein the medicament is to be locally administered into the patient's bladder from 20 mg/day to 300 mg/day of the gemcitabine for up to 7 days.

12. A drug delivery device comprising a medicament according to any one of the preceding claims, configured to locally administer the gemcitabine into the bladder continuously over a period of at least 6 hours, when the drug delivery device is to be inserted into the bladder, wherein the device is configured to release the gemcitabine into the bladder in an amount therapeutically effective for the treatment of prostate cancer, wherein the device is configured to release gemcitabine into the bladder at a mean average amount of from 1 mg/day to 300 mg/day of the gemcitabine .

13. Use of gemcitabine in the manufacture of a medicament for treatment of prostate cancer in a patient in need thereof, wherein the medicament is to be locally administered into the bladder of the patient to achieve a sustained concentration of the gemcitabine in urine in the bladder sufficient to produce a therapeutic concentration of the gemcitabine in the prostate, and wherein the medicament is to be locally administered into the bladder continuously over a period of over 6 hours.

14. The use of claim 13, wherein at least a second therapeutic agent is to be administered to the patient.

15. The use of claim 14, wherein the second therapeutic agent is to be administered intravesically.

16. The use of claim 14 or 15, wherein the second therapeutic agent comprises a cytotoxic agent, an analgesic agent, an anti-inflammatory agent, or a combination thereof.

17. A medical device comprising:

a housing configured for intravesical insertion; and

a dosage form comprising gemcitabine,

wherein the housing holds the dosage form and is configured to release the gemcitabine into the bladder in an amount therapeutically effective for the treatment of prostate cancer, wherein the device is configured to release gemcitabine into the bladder at a mean average amount of from 1 mg/day to 300 mg/day of the gemcitabine, and wherein the device is configured to release gemcitabine into the bladder continuously over a period of over 6 hours.

18. The device of claim 17, wherein the gemcitabine contained in the housing is in a non-liquid form.

19. The device of claim 17, wherein the housing is elastically deformable between a retention shape configured to retain the device in a patient's bladder and a deployment shape for passage of the device through the patient's urethra.

20. The device of any one of claims 17 to 19, which is configured to release from 1 mg/day to 100 mg/day of the gemcitabine for up to 7 days.

21. The device of any one of claims 17 to 19, which is configured to release from 20 mg/day to 300 mg/day of the gemcitabine for up to 7 days.