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Nanotechnology in Urology

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Abstract

Nanomedicine is a new distinct scientific discipline that explores applications of nanoscale materials (1–1000 nm) for various biomedical applications. At nanoscale, the physical properties of materials are altered as well as their interactions with cells and tissue. This occurs primarily because of the significant difference in the surface area-volume ratio as materials are reduced to nanosized level¹. Nanomedicine explores nanotechnology for monitoring, repair, and control of human biological systems at cellular and molecular levels using engineered nanodevices and nanostructures². Nanomedicine thus can improve diagnosis and treatment, and it can also be used in tissue engineering to replace some functions of human organs. The potential scope of nanotechnology in urology is wide-ranging, from prevention to early detection, treatment, prognosis, and symptom management³. The most common nanoscale drug delivery and imaging vehicles (nanocarriers) include polymeric nanoparticle, dendrimers, nanoshells, liposomes, nucleic acid based nanoparticles, magnetic nanoparticle, and virus nanoparticles⁴. This review summarizes some of the emerging applications of nanomedicine in urology.

Keywords

Nanoparticles; Drug Delivery; Cancer; Imaging; Anti-cancer drugs

1. Application of nanotechnology for diagnosis

1.1 Application of nanotechnology for imaging

Applications of nanotechnology in the diagnosis of genitourinary diseases have been extensively studied in recent years. Advances in nanotechnology have shown the promise of nanoparticles for noninvasive tumor imaging. Noninvasive imaging approaches, such as x-ray–based computer-assisted tomography (CT), positron emission tomography (PET), single-photon emission tomography, and magnetic resonance imaging (MRI), are used as important tools for detection of human cancers. The development of tumor-targeted contrast agents based on nanoparticle formulations have been shown to increase the sensitivity and specificity of tumor imaging using currently available imaging modalities⁵. Superparamagnetic iron oxide (SPIO) or iron oxide (IO) nanoparticles are becoming increasingly attractive as the precursor

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for the development of target-specific MRI agents. Magnetic nanoparticles (MNPs) can shorten both the T1 and T2 and enhance MR contrast. However, T1 shortening processes require a close interaction between protons and T1 agents which can be hindered by the thickness of the coating on the MNP. The T2 shortening due to the large susceptibility difference between the particles and surrounding medium⁵.

MNPs can extravasate into the interstitial space and subsequently transported to lymph nodes where they are taken up by macrophages. This can be used to detect lymph node metastasis⁶. Within the lymph nodes, lymphotropic superparamagnetic nanoparticles are internalized by macrophages and change magnetic properties detectable by MRI⁷. Renal carcinoma (RCC) is the third common genitourinary tumor⁸. The lymphatic metastasis is associated with patient's survival; therefore it is important to improve the detection of nodal metastases. MRI is widely used to diagnose renal cancer. Although it provides images with excellent anatomical details and soft tissue contrast but is relatively insensitive to detect lymph-node metastases⁹. Therefore, lymphotropic nanoparticle-enhanced magnetic resonance imaging (LNMRI) has been used to identify malignant nodal involvement in patients with renal neoplasm. In one study, monocrystalline iron oxide magnetic nanoparticles were administered by intravenous method, and imaging was performed before, immediately and 24 hours after administration. LNMRI showed high sensitivity (100%) and specificity of detection of lymph node metastasis (95.7%)¹⁰.

Prostate cancer is one of the most common cancers in north America¹¹. After the diagnosis of prostate cancer, accurate detection of lymph-node metastases is essential to determine the extent of the disease in order to select appropriate therapy. Patients with local prostate cancer can receive radical prostatectomy, watchful waiting, or radiotherapy; however, patients with advanced or metastatic prostate cancer require an adjuvant androgen-deprivation therapy. Nanoparticles are used to detect the nodal metastases in patients with prostate cancer. In one study, all patients with nodal metastases were identified by MRI with lymphotropic superparamagnetic nanoparticles, and node-by-node analysis showed MRI with nanoparticles had a significantly higher sensitivity than conventional method (90.5% vs 35.4%, $P < 0.001$)⁶. LNMRI is also used to detect the metastases within retroperitoneal nodes in patients with testicular cancer; the sensitivity, specificity and accuracy of LNMRI for malignant lymph node involvement was 88.2%, 92%, and 90.4%, respectively. On the other hand, the sensitivity, specificity and accuracy of size criteria for detecting malignant nodes was 70.5%, 68%, 69% respectively¹¹. These clinical trials suggest promising future of applications of LNMRI in urology.

Recently, Jain et al. have developed biocompatible magnetic nanoparticles with dual functional properties. The iron-oxide core is first coated with oleic acid (OA) and then OA-coated particles are stabilized with pluronic F127 to make them dispersible in aqueous vehicle. Pluronic prevents protein binding and particles aggregation that reduces their rapid clearance by the reticulo-endothelial system, keeping nanoparticles in systemic circulation to allow their extravasation into tumor tissue. Doxorubicin (base form) and paclitaxel were shown to load these nanoparticles with high efficiency (75–95%), and the loaded drugs are released over two weeks, thus sustaining the drug effect. Further, a combination of drugs can be loaded in these nanoparticles for synergistic activity. These multifunctional nanoparticles have greater advantage as compared to conventional magnetic nanoparticles as these can be used for both drug delivery and imaging applications (Figure 1)^{12–14}.

Semiconductor quantum dots (QDs) are nanometer-scale, light-emitting particles, which have some unique optical and electronic properties such as size-tunable light emission, improved signal brightness, enhanced stability of the fluorescent signal, and the ability to simultaneously excite multiple fluorescent colors¹⁵. These characteristics make QDs to have broad absorption,

narrow and symmetric emission spectra, long-term photostability, and continuous absorption spectra, and easy to be used as probes for multicolor imaging compared to conventional dyes^{16, 17}. Gao et al. developed bioconjugated QD probe suitable for *in vivo* targeting and imaging in mice. The conjugated QD contained an amphiphilic triblock copolymer for *in vivo* protection, antibody to target prostate specific membrane antigen (PSMA) and multiple PEG molecules to improve biocompatibility and circulation. Imaging study *in vivo* demonstrated the QD probes can be targeted to prostate tumor sites in mice through both passive and active mechanism, but passive targeting is much slower and less efficient than active targeting¹⁸.

1.2 Application on nanotechnology for detection of single nucleotide polymorphism

Progresses in nanotechnology allowed detection of single nucleotide polymorphisms (SNPs) in genes related to cancer, genetic disease and nitrification^{19–22}. Autosomal dominant polycystic kidney disease (ADPKD) is a genetic disease of human. ADPKD is characterized by enlarged polycystic kidneys and results in end-stage renal disease. ADPKD is caused by mutations of two genes: PKD1 and PKD2^{23, 24}. Son et al. have developed a rapid, accurate, and inexpensive nanoparticle-DNA based assay to detect PKD SNPs mutations in hybridizations-in-solution platform. The Fe₃O₄/Eu:Gd₂O₃ and Fe₃O₄/Tb:Gd₂O₃ core-shell nanoparticles were used to encapsulate DNA. The PKD SNPs from kidney tissue and blood samples can be detected without PCR step, which is convenient. The sensitivity of this method is very high and for blood genomic DNA, only 0.02–0.05 ml of whole blood sample needed for detection²⁵.

1.3 Application of nanosensor for bacterial detection

Basu et al. developed a quick and sensitive procedure for bacterial detection in case of kidney infection. The procedure is based on both optical and electrochemical studies. Detection method used gold nanowire devices in conjunction with a linker arm attached to specific *E.coli* antibodies. The study showed that the biosensor can detect each of 50 *E.coli* cell with the sensor area of 0.178 cm²²⁶.

2. Application of nanotechnology for treatment

2.1 Nanocarrier delivery of drugs for treatment of urological cancers

Nanoscale vehicles have been extensively investigated to delivery anticancer drugs. The most common examples of the nanoscale delivery vehicles include polymeric nanoparticles, dendrimers, nanoshells, liposomes, nucleic acid based nanoparticles, magnetic nanoparticles, and virus nanoparticles²⁷. Current chemotherapeutic drugs not only kill cancer cells, but also healthy cells and cause significant toxicity to patients. The nanocarrier-based delivery of anticancer drugs to tumor tissue can be achieved by either passive or active targeting; hence these methods of drug delivery can increase the effect of drug while reducing side-effects. Tumors tissue has leaky blood vessels and poor lymphatic drainage. While free drugs may diffuse nonspecifically, a nanocarrier can extravasate into the tumor tissue via the leaky vessels by the enhanced permeability and retention (EPR). The dysfunctional lymphatic drainage in tumor facilitates nanocarriers to accumulate in tumor tissue and release drugs into the vicinity of the tumor cells. Active targeting tumor cells achieved by conjugating nanocarriers containing chemotherapeutics with molecules that bind to overexpressed antigens or receptors on the target cell²⁸.

Drug resistance is one of the major obstacles limiting the therapeutic efficiency of chemotherapeutic or biologic agents. The mechanism of cancer drug resistance is complex. More often, it is due to the over-expression of Multidrug Drug Resistance (MDR) transporters; the transporters actively pump chemotherapeutic drugs out of the cell and reduce the

intracellular drug dose below lethal threshold levels²⁷. Nanocarriers can bypass the MDR by preventing anticancer drugs to encounter the transporters. Sahoo and Labhasetwar studied cytotoxicity of transferrin-conjugated (Tf-Tx-NPs) and unconjugated paclitaxel loaded nanoparticle (Tx-NPs) *in vitro* in drug resistant cell lines. They found the conjugated nanoparticle can overcome drug resistant by sustaining intracellular drug retention²⁹.

7-Ethyl-10-hydroxy-camptothecin (SN-38) is a biological active metabolite of irinotecan hydrochloride (CPT-11) and has potent antitumor activity. Sumitomo et al. used SN38-incorporated polymeric micelles, NK012 to treat the renal cell carcinoma model established by inoculating murine Renca cells and human renal cancer cells SKP-9. Compared with CPT-11, NK012 was shown to have significantly higher antitumor activity against both bulky Renca tumors and SKRC-49 tumors than drug alone. In the pulmonary metastasis model, administration of NK012 enhanced and prolonged distribution of free SN-38 in metastatic lung tissues, meanwhile, the concentration of SN-38 in nonmetastatic lung tissues was much lower. NK012 treatment decreased the metastatic nodule number significantly. These results demonstrate the significant advantages of polymeric micelle-based drug carriers and the authors suggested that NK012 would be effective in treating disseminated renal cancer with irregular vascular architectures³⁰.

Current treatment of superficial bladder cancer consists of transurethral tumor resection and chemotherapy. Chemotherapy usually follows surgery to reduce tumor recurrence and/or progression. Intravesical chemotherapy can selectively deliver drugs to bladder while minimizing systemic exposure. However, the response of intravesical chemotherapy is incomplete and variable among patients; this is partly due to the inability of drug to penetrate bladder tissue. Chemotherapeutic drugs loaded nanocarriers provide more efficient and specific approaches to treat bladder cancer than drug alone. Paclitaxel for clinical use is dissolved in Cremophor; however, it reduces the free fraction of paclitaxel and consequently lowers the drug penetration into the bladder tissue. Lu et al. developed paclitaxel-loaded gelatin nanoparticles for intravesical delivery to increase the penetration of paclitaxel into bladder tissue. The paclitaxel-loaded gelatin nanoparticles can release the drug rapidly, resulting in much higher drug concentrations in the urothelium and lamina propria than with Cremophor formulation³¹. Bladder transitional cell carcinoma over-expresses the transferrin receptors on the surface of cells. Derycke et al. examined penetration and accumulation of transferrin-mediated liposomal targeting of the photosensitizer, aluminum phthalocyanine tetrasulfonate (AlPcS4) in bladder tumor. AlPcS4 was encapsulated in unconjugated liposomes (Lip-AlPcS4) or transferrin-conjugated liposomes (Tf-Lip-AlPcS4). The accumulation of free AlPcS4, Lip-AlPcS4, and Tf-Lip-AlPcS4 in human AY-27 transitional-cell carcinoma cells and in an orthotopic rat bladder tumor model was visualized by fluorescence microscopy. Results showed accumulation of Tf-Lip-AlPcS4 was much more than that of Lip-AlPcS4 (384.1 versus 3.7 μ M; $P=0.0095$). The *in vivo* study showed that intravesical instillation of Tf-Lip-AlPcS4 resulted in specifically accumulation of AlPcS4 in tumor tissue whereas instillation of free AlPcS4 resulted in nonselective accumulation throughout the whole bladder wall whereas instillation of Lip-AlPcS4 resulted in no tissue accumulation. Photodynamic therapy of AY-27 cells showed Tf-Lip-AlPcS4 had high cytotoxicity. The results suggested that transferrin-mediated liposomal targeting of photosensitizing drugs is a promising potential tool for photodynamic therapy of superficial bladder tumors³². Submucosal injection of doxorubicin-loaded liposome in bladder was shown to result in better distribution of drug and prolonged retention through the bladder wall and regional lymphoid nodes compared to free drug. The result suggests that the therapeutic use of nanocarrier not only in superficial bladder cancer but also in invasive bladder cancer and regional lymphoid node metastasis³³.

Because of its high mobility, prostate cancer always causes great interest to researchers. There are several examples of applications of chemotherapeutic drug loaded nanocarriers for treating

prostate cancer. Doxorubicin-loaded micelle and curcumin-loaded liposomes have been shown to improve the efficacy over free drugs^{34, 35}. It has been shown that A10 2'-fluoropyrimidine RNA aptamer (Apt) can bind to the prostate specific membrane antigen (PSMA). A combination of Apt and antibody against PSMA (J591) conjugated to nanoparticles was shown to significantly improve the uptake of nanoparticles by PSMA (+) prostate cancer cells (Figure 2)^{36–38}. In another approach, the fact that transferrin receptors are over-expressed on the surface of prostate cancer cells was used to improve drug delivery. Sahoo et al. used transferrin conjugated sustained release paclitaxel-loaded biodegradable nanoparticles to treat prostate cancer. The *in vivo* experiment in subcutaneous animal model via direct intratumoral injection of transferrin-conjugated nanoparticles showed complete tumor regression compared to paclitaxel-Cremophor[®] and paclitaxel-loaded nanoparticle without transferrin (Figure 3)²⁸. The efficacy of transferrin-conjugated nanoparticles is suggested to be due to enhanced cellular drug uptake and sustained drug retention in tumor tissue. Direct intratumoral injection of drug-loaded nanoparticles can be effective in the treatment of localized tumor such a prostate or kidney tumors and could a prefer option over surgical intervention to remove tumor.

The possibility of thermal therapy of prostate cancer with nanocarriers is another interesting approach, particularly to treat the cancer which is refractory to chemotherapy. Kawai et al. examined the hyperthermic effect of magnetic particles in rat prostate cancer. Magnetic liposomes (MCLs) generate heat in an alternating magnetic field (AMF). The tumor temperature can increase to 45 °C whereas the body temperature remains at around 38 °C. Significant tumor regression was observed in the hyperthermic group. Immunohistochemical staining showed the presence of CD3, CD4, and CD8 immunocytes in the tumor tissues of the rats exposed to hyperthermia. Heat shock protein 70 also appeared in the viable area at its boundary with the necrotic area³⁹. Further study showed MCL+AMF heat therapy suppressed tumor growth in bone microenvironment; however, almost half of the animals which received MCL+AMF treatment died. This method has some side effects and need further study⁴⁰. Gold nanoshells (GNS) are designed to absorb near infrared (NIR) light that strongly generate heat and provided optically guided hyperthermic ablation. Laser activated GNS have been shown to kill human prostate cancer cell PC-3 and C4-2 *in vitro*⁴¹, and *in vivo* study with ectopic murine prostate cancer model with laser activated GNS caused 93% necrosis and regression in the high dose of GNS treated mice⁴².

Several clinical trials of nanocarrier-based delivery of chemotherapeutic drugs are underway. One multi-institutional phase II trial of pegylated-liposome doxorubicin in the treatment of locally advanced unresectable or metastatic transitional cell carcinoma of the urothelial tract showed clinical response rate and favorable toxicity profile⁴³. Liposomal doxorubicin was used to treat hormone-refractory prostate cancer, which is a challenge to urologists. The Phase I study in which liposome-encapsulated doxorubicin was used to treat patients with advanced, androgen-independent prostate cancer did not show clinical response, that may be due to the low dosage⁴⁴. However, in another prospective randomized phase II trial, patients with symptomatic hormone-refractory prostate cancers were treated with pegylated liposomal doxorubicin at 25 mg/m² every 2 weeks for 12 cycles (Group A) or 50 mg/m² every 4 weeks for 6 cycles (Group B). Decrease of prostate surface antigen (PSA) level was observed in 25.8% patients in group B, the mean time to disease progression was 6.5 months, Patients in Group B had a significantly higher rate of pain relief, and the mean 1-year survival rate was also significantly higher. Toxicity types differed significantly between Group A and Group B, but no dose-limiting cardiotoxicities or hematotoxicities were found⁴⁵.

2.2 Nanocarrier delivery of drug for no-cancer diseases

Nanocarrier delivery of drug not only can be used to treat cancer but also to benign diseases. The effect of liposomes prepared from various natural and synthetic lipids on attenuating

hyperactivity in bladder irritation was studied. Liposome of uncharged zwitterionic phospholipids significantly attenuated the irritation and decreased bladder contrast frequency caused by protamine sulfate but empty liposomes were not able to achieve the same effect⁴⁶.

Effect of intraurethral application of Prostaglandin-E1 (PGE1)-loaded liposome was compared to that of intracavernosal injection of PGE1 for treating psychogenic and organic erectile dysfunction (ED). The intraurethral application of liposomal PGE1 was not effective in patients with organic ED. However, in 60% patients with psychogenic ED, it was effective enough, thus it might be a convenient and painless therapeutic alternative for selective group patients⁴⁷. Foldvari et al. tested the effect of transdermal delivery of liposome encapsulated PEG1 in patient with ED. The study was carried out in 5 patients in a double-blind, placebo-controlled fashion. Application of two transdermal PEG1 formulations caused peak systolic flow velocities in the deep cavernosal arteries of patients increased significantly. The highest mean peak systolic flow velocity was achieved at 45 minutes after application. Formulation of liposome with encapsulated PEG 1 showed 7-fold increase mean peak flow velocity compare with baseline values following transdermal application of the formulation, and thus could be a promising approach for the treatment of erectile dysfunction⁴⁸.

Significantly improved survival of rats with renal transplantation was shown following intravenous administration of bilayer liposomes encapsulated methylprednisolone once a week. Daily administration of the same dose of free drug could result in similar survival, but urine analysis showed a consistently higher protein excretion and retention of creatinine and urea in free drug group. Compared to free methylprednisolone, liposome encapsulated methylprednisolone may be selectively inhibited T-cell activation and cytokine production. The expression of CD45RC, CD25, IL-2, IL-7, IL12, TNF- α , INF- γ was strongly inhibited in drug encapsulated group⁴⁹.

2. 3 Nanocarrier for delivery of genes

Gene therapy refers to the transfer and expression of genes of therapeutic applications in the target cells, is regarded as a potential revolution in medicine⁵⁰. The application of gene therapy promises progress in understanding physiological roles of genes and in treating diseases at the genetic level. The ectopic expression of foreign genes is the most critical aspect for the success of in vivo gene expression and therapy. The vectors, which protect the ectopic genetic material and ferry it to the cells, are classified into two categories: viral and nonviral⁵¹. Viral vectors have efficient cell-entry mechanism; however, these viral vectors have several major restrictions, such as limited DNA-carrying capacity, lack of target-cell specificity, immunogenicity and some viral vectors, and the risk of insertional mutagenesis⁵². Nonviral vectors are relatively simple to synthesize and have less risks than their viral counterparts have. In addition, the nonviral vectors have no limitation of the size and number of the genetic inserts⁵¹. Nanocarriers are promising to be used as nonviral vectors.

Prabha and Labhasetwar studied the parameters that influence the efficacy of nanoparticle-mediated gene transfection. The results showed the DNA loading in nanoparticle and its release, and surface properties of nanoparticles are the critical determinant in nanoparticle-mediated gene transfection⁵³. Larchian et al. developed a liposome-mediated immune-gene therapy using interleukin 2(IL-2) and B7.1 in MBT-2 mouse bladder cancer model. The study showed that the liposome-mediated transfection is safe, simple and highly effective compared with retroviral system⁵⁴. Herpes simplex virus thymidine kinase (HSV-tk) gene delivered by Folate-linked, lipid-based nanoparticles can achieve high transfection efficiency and selectivity, inhibiting tumor growth following intratumoral injection into prostate cancer⁵⁵.

3. Application of nanotechnology in tissue engineering of urology

The epidemic of end-stage renal diseases (ESRD) continues worldwide, nearly 900,000 patients are currently on dialysis or surviving with a functioning kidney transplantation⁵⁶. The majority treatment of ESRD is intermittent haemodialysis. However, haemodialysis has high mortality and morbidity for long-term use. Nissenson et al. applied nanotechnology to develop a renal replacement device, the human nephron filter (HNF), which might significantly improve the current outcomes and quality of life of ESRD patients. The HNF consist of two membranes operating in series within one cartridge. The first membrane, the G membrane mimics the function of the glomerulus. Plasma ultra filtrate generated by using convective transport contains all solutes approaching the molecular weight of albumin. The second membrane is the molecularly engineered T membrane that mimics the function of the renal tubules. The HNF could provide the equivalent of 30 ml/min of glomerular filtration rate if operated for 12 hours per day (Figure 4). The instrument is wearable and can permit full mobility and improve patient quality of life significantly⁵⁶.

Pattison et al. developed three-dimensional, porous, degradable poly (lactic acid-co-glycolide) (PLGA) and poly (ether urethane) (PU) scaffolds having nano-rough surface topographies. Human bladder smooth muscle cells seeded on these scaffolds showed increased cell adhesion, growth, and protein production compared those seeded on the conventional, micro-dimensional scaffolds. The results suggested the nano-dimensional polymeric scaffolds are promising replacement materials for human bladder wall^{57, 58}.

4. Summary

Translational nanomedicine is undergoing rapid transition from development and evaluation in laboratory animals to clinical practices. In the future, it is anticipated that nanotechnology can provide urologists a new point of view to understand the mechanism of disease, tools for early diagnosis of the disease, and effective modality for treatment.

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Figure 1.

A) Schematic of oleic acid –Pluronic –coated iron oxide magnetic nanoparticles. **B)** Particle size analysis of magnetic nanoparticles. Mean diameter of the core is ~12 nm whereas hydrodynamic diameter is around 190 nm. Reproduced from Jain et al. *Mol Pharmaceutics*. 2008;5:316–27

Figure 2.

NP-Apt cellular uptake. The nitrobenzoxazole (NBD) dyes (green) were encapsulated into PLGA-PEG-aptamer triblock nanoparticles. Left 2 pictures are LNCaP (PSMA+) cells, right 2 pictures are PC3 (PSMA-) cells. Cells were incubated with 50 μ g of NBD encapsulated PLGA-PEG-aptamer nanoparticles for 30 min. Reproduced from Gu et al. PNAS 2008;105(7): 2586–91

Figure 3.

A) Paclitaxel-loaded PLGA nanoparticles. Bar indicates 100 nm. **B)** Antitumor activity of Tx-NPs-Tf (paclitaxel-loaded transferrin conjugated nanoparticles) in a murine prostate tumor model. PC3 cells (2×10^6 cells) were implanted s.c. in athymic nude mice. Tumor nodules were allowed to grow to diameter of about 50 mm³ prior to receiving different formulations as a single-dose treatment. Tx-NPs-Tf (●, 24 mg/kg; □, 12 mg/kg), Tx-NPs (×, 24 mg/kg), Tx-Cremophor® EL formulation (▲, 24 mg/kg), (◆) control NPs and (■) Cremophor® EL formulation. Data are means $\pm$ s.e.m., $n=6$. $p < 0.005$ Tx-NPs-Tf versus Tx-NPs and Tx-Cremophor® EL groups. Figure A reproduced from Sahoo and Labhasetwar. *Mol Pharmaceutics* 2005;2(5):373–83 and B from Sahoo et al. *Int J Cancer*, 2004;112(2):335–40.

Figure 4.

Blood flows across the G membrane that create an ultrafiltrate which is then passes over the T membrane. The needed solutes and water passed through molecularly engineered pores is returned to the blood while the remainder of the ultrafiltrate is collected in the drainage bag. Reproduced from Nissenson et al. Hemodial Int 2005; 9: 210–7