Review Article

Nanotechnology in Urology

Sudhindra Jayasimha*

Department of Urology, CMC, Vellore, Tamil Nadu, India

*E-mail: sudhindra.j@gmail.com

ABSTRACT

Introduction: Nanotechnology has revolutionized our approach to medical diagnostics as well as therapeutics and has spanned an entirely new branch of research. This review addresses the potential applications of Nanotechnology in Urology. This article is based on the Dr. Sitharaman Best Essay award of the Urological Society of India for 2016.

Methods: A PubMed search was performed for all relevant articles using the terms, "nanotechnology, nanoparticles, nanoshells, nanoscaffolds, and nanofibers."

Results: The developments in diagnostics include novel techniques of imaging of genitourinary malignancies, prostate-specific antigen measurement, early detection of mutations that are diagnostic for polycystic kidney disease. The potential applications of nanotechnology are in the targeted therapy of genitourinary malignancies, erectile dysfunction, overactive bladder, bladder reconstruction, construction of artificial kidneys and biodegradable stents as well as in robotic surgery.

Conclusions: Nanotechnology is a rapidly emerging branch of research in urology with diverse and clinically significant applications in diagnostics as well as therapeutics.

INTRODUCTION

From time immemorial, man has been fascinated by the subatomic world. From the Vedas that mention the "Paramanu" or the atom to the discovery of "Animalcules" (protozoa) by Antoni van Leeuwenhoek, the quest to understand the microscopic world and harness its capabilities has continued unabated. This has led us to the science of nanotechnology which may be defined as the study of man made particles from 1 to 1000 nm in diameter. Nanotechnology involves investigation, construction, control, and manipulation of biological systems at the molecular level. The possibilities that nanotechnology offers in terms of diagnosis, therapy, and reconstruction to medicine in general and urology in particular are limited only by our imagination. This article aims to review the potential applications of Nanotechnology in Urology. It is based on the Dr. Sitharaman Best Essay award of the Urological Society of India for 2016.

METHODS

A PubMed search of all articles using the terms nanotechnology, nanoparticles, nanoshells, nanoscaffolds, and nanofibers was performed and relevant articles were selected for this review. The following developments were identified for further elaboration: Imaging of genitourinary malignancies, prostate-specific antigen (PSA) screening, treatment of genitourinary malignancies, reconstruction of the bladder, treatment of interstitial cystitis and overactive bladder, tissue sealant technology and robotic surgery, treatment of erectile dysfunction, biodegradable stent technology, artificial kidney and detection of genetic mutations.

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IMAGING OF GENITOURINARY MALIGNANCIES

Computed tomography (CT) and magnetic resonance imaging (MRI) are the most commonly used imaging modalities for the staging of genitourinary cancers. Tumours are diagnosed based on morphological appearance which may be inaccurate due to the resolution.[1] Intravenous iron oxide (IO) or superparamagnetic IO may be administered intravenously to improve accuracy in this regard. These nanoparticles extravasate into the interstitium of the tumors because of basement membrane abnormalities and decreased pericytes around the tumor capillaries.[2] Most tumor vessels show 200–900 nm gaps between the endothelial cells.[3] The IO nanoparticles that extravasate are transported to the lymph nodes where they are taken up by macrophages. This changes the electromagnetic properties of the nodes which can be detected on MRI.[4] Gadolinium as well as gold nanoparticles with biotin and methoxy-terminated ligand bound with streptavidin-fluorophore dye helps in retention of these particles within the tissues and an increase in sensitivity by 2.46 times.[5] Lymphotropic nanoparticle-enhanced MRI has been shown to have a sensitivity of 100% and specificity of 95.7% in the detection of nodal metastasis in renal cell carcinoma.[6] In case of prostate carcinoma, the sensitivity was 90.5%[7] while in testicular malignancy, the sensitivity, specificity, and accuracy were 88.2%, 92%, and 90.4%, respectively.[8]

Nanotechnology has also challenged the current knowledge of lymphatic drainage in genitourinary cancer. Tc 99 was injected into each lobe of the prostate, and after 1 h, scintigraphy as well as CT was performed. Fusion images detected a mean of 10 nodes per patient with the locations of primary drainage sites being common iliac in 16%, internal iliac in 19%, external iliac in 33%, obturator group in 26%, para-aortic in 4%, and presacral/inguinal in 1% each. This suggests that the extent of lymphadenectomy in radical prostatectomy may need to be redefined.[9]

Quantum dots (QDs) are semiconductor nanoparticles that are fluorescent. They have a long half-life, narrow emission wavelength that can be adjusted with size (650–950 nm) and photostability. They can excite multiple fluorescent colors simultaneously which make them suitable as probes for multicolor imaging.[10] Carboxymethyl chitosan (CMC) labeled QDs show affinity for zinc which is a regulator in prostatic cells. CMC labelling increases the affinity of QDs for zinc in prostatic cancer tissue and improves detection of the same. While CMC labelling enhances the optical signal of QDs, in addition it also reduces potential toxicity of the semiconductor core.[11] Similarly, QDs labeled with antibodies to prostate-specific membrane antigen (PSMA), amphiphilic triblock copolymer (for *in-vivo* protection), and polyethylene glycol (for biocompatibility) have been developed. These probes have been shown to target prostate cancer sites in mice by active as well as passive mechanisms.[12] While QDs offer exciting diagnostic opportunities, the potential toxicity remains to be further investigated.

PROSTATE-SPECIFIC ANTIGEN SCREENING

A gold nanoparticle-based bio-barcode assay has been described that helps in the detection of PSA recurrence after radical prostatectomy. It is 300 times more sensitive than conventional assays and may help in detection of hitherto undetectable PSA levels after radical prostatectomy. This will translate into early detection of biochemical recurrence and timely salvage therapy may then be initiated to improve survival.[13] Microcantilevers that bend with the deposition of PSA on the surface have also been reported in the optical assay of ultra-low concentrations of PSA.[14] Gold nanoparticles labeled with antibodies can detect PSA levels as low as 1 pg/ml due to the intense surface-enhanced Raman scattering.[15]

TREATMENT OF GENITOURINARY CANCER

The role of nanoparticles in drug delivery and cancer therapeutics is probably the best-studied application of nanotechnology. Various drug delivery vehicles have been described including liposomes, spheres, tubes, nucleic acids, magnetic particles, polymers, dendrimers, nanoshells, viral vectors, and composite molecules.[16] The current chemotherapy is limited by its toxicity on healthy tissues – nanotechnology offers selective targeting of cancer cells by passive or active methods with improved therapeutic index and lower toxicity. Cancer cells have porous capillaries with wider intercellular pores and poor lymphatic drainage which allows nanoparticles to accumulate passively in these tissues.[2] Conjugated nanoparticles can bind to receptors/antigens on the target cell in an active fashion.[17] Nanoparticles larger than 10 nm are not cleared by the kidneys and may prevent nephrotoxicity due to drugs such as cisplatin, with comparable activity.[18]

Drug resistance is the bane of cancer chemotherapy today. One of the mechanisms of resistance is multidrug resistance (MDR) transporters that actively transport drugs outside the cell and reduce their intracellular concentration. Transferrin-conjugated paclitaxel has been shown to overcome the MDR transporters and sustain intracellular levels in a murine model of prostate cancer.[17]

The current therapy of non-muscle invasive bladder cancer involves transurethral resection of tumors, followed by intravesical therapy. The individual response to intravesical therapy is variable due to the inability of drugs to

penetrate bladder epithelium. Paclitaxel-loaded gelatin nanoparticles overcome this limitation and show high concentration in lamina propria compared to the current formulations of paclitaxel with Cremophor.[19] Transitional epithelium expresses transferrin receptors which may be targeted by transferrin-labeled liposome encapsulating photosensitizer – aluminum phthalocyanine tetrasulfonate. Intravesical instillation of the same showed specific uptake by tumor epithelium in *in-vivo* studies and may be used in photodynamic therapy of bladder tumors.[20] Submucosal injection of liposomes loaded with doxorubicin showed better epithelial drug retention as well as regional nodal uptake in bladder tumors.[21] This may provide a therapeutic alternative in invasive bladder tumors. Coumarin-loaded polylactide-co-glycolide nanoparticles were modified with the addition of poly guanidinium oxanorbornene. When the histone deacetylase inhibitor belinostat was loaded onto this nanoparticle, the penetration of bladder mucosa improved 10-fold and there was a 70% volume reduction in cultured bladder tumor cells.[22] In a phase II trial, pegylated liposomal doxorubicin was shown to have a 20% response rate with no cardiac or hematological toxicity in the treatment of metastatic/unresectable upper tract transitional cell carcinoma (TCC). This makes a case for the addition of or substitution with pegylated liposomal formulation of doxorubicin in the treatment of upper tract TCCs.[23]

7-ethyl-10-hydroxycamptothecin (SN-38) is an active metabolite of irinotecan that is of therapeutic potential in renal cell carcinoma. Polymeric micelles containing SN-38 showed better activity against bulky primary tumors as well as pulmonary metastases as compared to irinotecan in the renal cell carcinoma model produces by inoculation of murine Renca with human renal cancer cells.[24] Interferon-beta gene incorporated into cationic multilamellar liposomes showed significant cytotoxicity by induction of apoptosis against renal cell cancer lines.[25]

Micelle-delivered doxorubicin has shown higher activity against rat prostate cancer cells due to its increased uptake and intracellular concentration compared to free doxorubicin.[26] Liposomal doxorubicin has been shown to accumulate and reach higher concentrations within tumor cells compared to the free drug.[27] Pegylated doxorubicin has been shown to produce a >50% PSA and pain score reduction in a phase II trial of castration-resistant prostate cancer when administered at a dose of 50 mg/m^2 every 4 weeks for six cycles. This effect was produced without the dose-limiting cardiac and hematological cytotoxicity of conventional doxorubicin.[28] Similarly, a docetaxel-encapsulated nanoparticle-aptamer bioconjugate has been shown to avidly target the PSMA with increased tumor cell and decreased systemic toxicity.[29]

Radiofrequency ablation and cryotherapy are now in vogue for the treatment of prostate cancer. However, they suffer from the drawbacks of nonuniform distribution of lethal temperature and incomplete ablation of tumor cells. Nanotechnology makes therapy cell specific and limits damage to normal tissue. In this respect, gold nanoshells (GNs) and carbon nanotubes (CNTs) have been designed for thermal ablation of prostate cancer. These nanoparticles absorb light in the near infrared spectrum (NIR) which excites the electrons in the outer orbits. When these electrons return to the prestimulation stage, energy is released as heat which in turn produces cell death.[30] When GNs were applied to prostate cancer cell lines PC-3 and C4-2, effective ablation was produced on exposure to NIR for 5 min.[31] When GNs were used as an intravenous formulation with PC-3 prostate cancer cell line, 93% of tumor necrosis was noted at 21 days.[32] CNTs have a broader absorption spectrum due to their larger mass and electron number. They are more efficient in heat production as compared to GNs.[33] When PC-3 prostate cancer cell line was incubated for 5 min with CNTs in the presence of NIR, there was 100% cell death with a 43° increase in temperature.[34] The one drawback of thermal ablation is that the nanoparticles are non-biodegradable and standard protocols on their use/biocompatibility are yet to be formulated.[35] However, no adverse effects have been reported in animal experiments thus far.

BLADDER RECONSTRUCTION

Traditional methods of bladder replacement use a segment of the intestine to replace the bladder which has its attendant metabolic and functional complications and a reduced quality of life. Moreover, they may be unavailable and donor-site healing may be problematic. The impermeable nature of the bladder mucosa to a high concentration of urinary solute, toxins, and bacteria also cannot be replicated. It is to this end that nanotechnology has been used to reconstruct the bladder. Three-dimensional, porous polylactide-co-glycolide and poly ether-urethane scaffolds were used to provide a framework for the growth of bladder smooth muscle. These scaffolds have nano rough surface topography that enhanced protein adsorption, cell adhesion, growth, and protein production.[36] Natural as well as a combination of natural and synthetic polymers may be used to electrospin and create these scaffolds.[37] An *in-vivo* animal study in a partial cystoplasty model showed early regeneration of urothelium as well as smooth muscle at 5 weeks and similar tensile strength to ileum.[38]

TREATMENT OF OVERACTIVE BLADDER/ INTERSTITIAL CYSTITIS

Intravesical therapy, while overcoming the side effects of anticholinergics such as dry mouth and constipation,

provides higher local drug concentrations and efficacy. Systemic toxicity is limited as the urothelium of the bladder is the most impermeable epithelial barrier of the body. Weekly intravesical empty liposomes (80 mg in 40 cc water) have been shown to ameliorate the symptoms of interstitial cystitis with decreased frequency, nocturia, and O'Leary-Sant symptom score. In this aspect, liposome therapy was found to be superior to oral pentosan polysulfate.[39]

Liposomes may also be used as a vector for botulinum neurotoxin. This improves the efficacy of the drug as uptake is better and degradation by proteases is prevented. Moreover, the need for intravesical injections can be circumvented as the efficacy remains the same which was demonstrated in the acetic acid rat model.[40] Imaging of interstitial cystitis is also aided by nanotechnology as liposomes and fluorescent nanoparticles bind to bladder lesions of interstitial cystitis which may be assessed by NIR imaging of the bladder.[41]

TISSUE SEALANT TECHNOLOGY AND ROBOTIC SURGERY

In laparoscopic and robotic surgery, hemostasis is achieved through diathermy/ultrasonic devices that produce collateral damage with charring and smoke production. To circumvent these drawbacks, the EnSeal™ system (Ethicon Endo-Surgery Inc., Cincinnati, OH) was introduced that uses millions of nanoparticles embedded in a bipolar temperature coefficient matrix. Sealing is achieved at temperatures below 100°C as the nanoparticles interrupt current flow above these temperatures. This reduces maximum mean temperature to 86.9F and collateral spread to 1.1 mm. Reduced collateral spread may protect the cavernosal nerve, urethral, and sphincter damage. EnSeal has been used to achieved hemostasis of the dorsal venous complex in robot-assisted laparoscopic prostatectomy as well as in laparoscopic nephrectomy.[42] Nanotweezers that could be used in vasectomy reversal and nanobots that could aid in cystoscopy, tumor fulguration, ureteroscopy, and inspection of the inferior vena cava for tumor thrombus are also in the early stages of development.[43]

TREATMENT OF ERECTILE DYSFUNCTION

Nanoparticles encapsulating tadalafil have been shown to produce significantly improved erections in rats when applied as a silane-based sol-gel formulation on the glans penis. It is believed that the nanoparticles which are 10 nm in diameter can overcome the skin barrier with 100 nm pores and pass into the venous channels that connect the glans with the corpora. These gel formulations may provide a more acceptable alternative to patients as they avoid intracorporeal injections and systemic side effects of these drugs.[44] Liposomal prostaglandin E1 formulations for intraurethral use with 60% efficacy have also been described.[45]

Nanotechnology has been used to address cavernosal nerve injury which is seen in diabetes, metabolic syndrome, and carcinoma prostate. Sonic hedgehog (SHH) gene has been shown to be produced in Schwann cells of cavernosal nerves, and it is believed to be essential for nerve repair. In rats, when SHH was delivered to cavernosal nerves using linear peptide amphiphile nanofiber gel injections, there was improved regeneration, reduced apoptosis, and 58% improvement in erectile function. This technique may be extended to the regeneration of any peripheral nerve in the future and may circumvent the systemic side effects of the current oral formulations used in erectile dysfunction therapy.[46]

BIODEGRADABLE STENT TECHNOLOGY

A poly-epsilon-caprolactone/polylactide-co-glycolide ureteric stent with nanofibers and micropores has been studied in a porcine model where it showed gradual degradation in a distal to proximal fashion in 10 weeks. When compared with commercial polyurethane stents, there was reduced pyuria and ureteric/vesical inflammation with the nanostructured stent. This has therapeutic potential in reducing tissue inflammation, edema, and the resultant symptoms in a patient.[47]

THE ARTIFICIAL KIDNEY

Chronic kidney disease is now an epidemic that has assumed global proportions. Against a demand of 20,000, only 3000 transplants were performed per annum in India in 2007.[48] The majority are on hemodialysis which has increased long-term morbidity. Nissenson Human Nephron Filter (HNF) is a portable artificial kidney that can be worn by the user.[49] It consists of two membranes within a cartridge – the first G-membrane produces an ultrafiltrate containing low molecular weight solutes approaching the weight of albumin, by convective transport. This mimics the function of the glomerulus. The second T-membrane performs the function of the renal tubules and resorbs select solutes to maintain homeostasis. The HNF is a product of molecular engineering which does not require a dialysate. It can provide a glomerular filtration rate of 30 ml/min and gives the patient mobility as well as improved quality of life.

Recently, researchers have described experiments where they seeded three-dimensional scaffoldings with rat neonatal kidney cells to construct the parenchyma and umbilical venous blood to reconstruct the endothelial component of the bioengineered kidney. Some functions were noted after implantation into rats which is a step forward in the direction of laboratory organ regeneration.[50]

GENE TRANSFER AND DETECTION OF SINGLE NUCLEOTIDE POLYMORPHISMS

Viral as well as nonviral vectors have been used to transfer segments of genes from one cell to another. Viral vectors have drawbacks such as insertional mutagenesis, immunogenicity, lack of specificity, and limited carrying capacity. It has been demonstrated that herpes simplex virus thymidine kinase delivery by folate-linked liposomes can inhibit tumor growth in prostate cancer. Similarly, interleukin-2 was delivered using liposomes for the immunotherapy of mouse bladder cancer. The nanoparticles may be engineered to deliver differing amounts of DNA to various tissue types which have potential in the treatment of various congenital and malignant disorders.

Nanotechnology can also be used to diagnose single nucleotide polymorphisms (SNPs). Fe3O4/Eu: Gd2O3 and Fe3O4/Tb: Gd2O3 core–shell nanoparticles have been used to develop a DNA assay which detects PKD-1 and PKD-2 SNPs in blood. These help in early, inexpensive detection of polycystic kidney disease and timely therapy.

CONCLUSIONS

Nanotechnology has changed the face of molecular diagnosis and therapeutics in urology. While some advances such as nanoscaffolds for tissue regeneration are early in their development, others such as superparamagnetic IO-based imaging, liposome, and gold nanoparticle-based drug delivery have reached clinical trials with promising early results in the diagnosis and treatment genitourinary malignancies. The development of highly sensitive assays improved by means of gene transfer and genetic diagnosis can help in timely diagnosis and treatment of various genetic and acquired disorders. In spite of its exciting prospects, nanotechnology is not without its risks as the nanoparticles, being able to pass through cell membranes, are a potential biohazard and the research on their toxicity is limited. The analogy is similar to that of nuclear power which is both a limitless source of energy and a tremendously destructive force. Stringent attention to patient safety and needs, regulations to prevent misuse and appropriate, timely translation to clinical research hold promise to change the face of healthcare in urology and bring the rewards of technology to the true beneficiary of all medical achievement, the patient.

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