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Theoretical Exploration of Nanoparticles Targeting Bacterial Prostatitis

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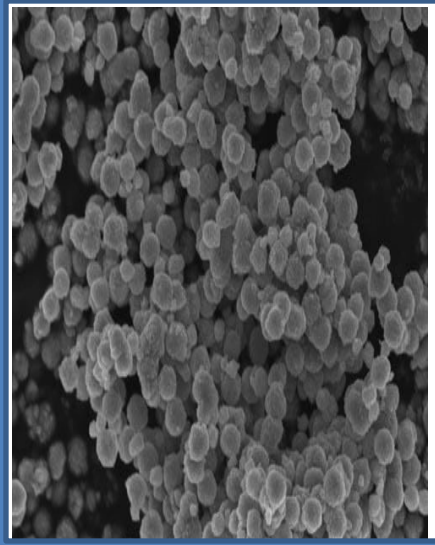
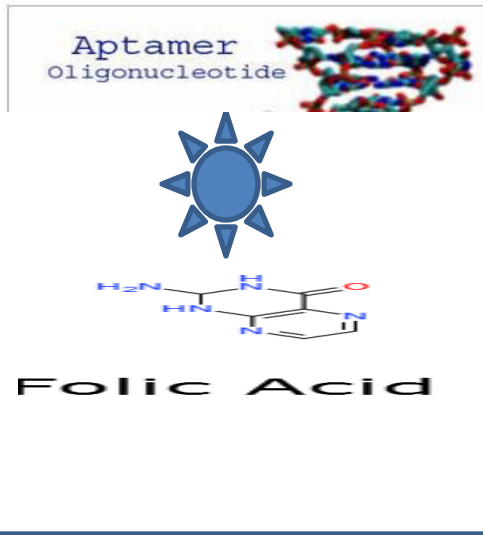
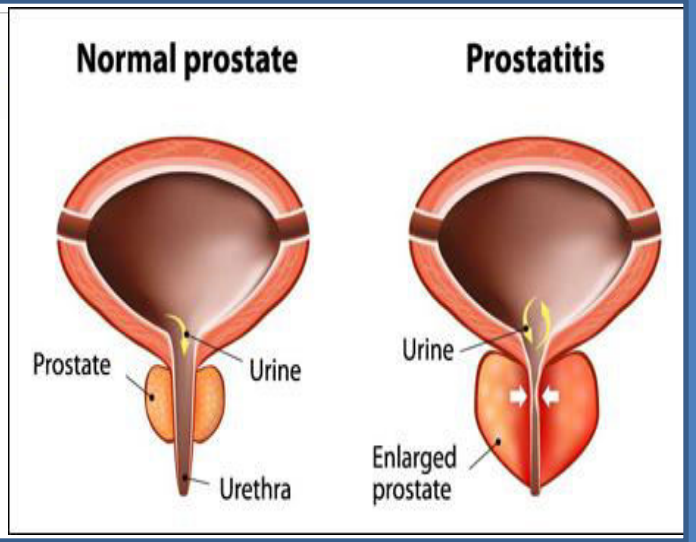
Graphical Abstract







Abstract:
Prostatitis describes a combination of infectious diseases (acute and chronic bacterial prostatitis), chronic pelvic pain syndrome (CPPS) or asymptomatic prostatitis Most men with “chronic prostatitis” have chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), characterized by pelvic pain. The etiology of this syndrome is not fully known, the evaluation has been controversial and treatment is, unfortunately, frequently unsuccessful. Focused multimodal therapy appears to be more successful than empiric monotherapy. In that sense, it is important to know how nanoparticles will function in an animal model. The present paper reviews promising methods to capture prostate targeting.

Keywords: Chronic Bacterial Prostatitis, Nanoparticles , Targeting.

Introduction

Prostatitis describes a combination of infectious diseases (acute and chronic bacterial prostatitis), CPPS or asymptomatic prostatitis. The NIH classification of prostatitis syndromes includes:

Category I: Acute bacterial prostatitis (ABP) which is associated with severe prostatitis symptoms, systemic infection and acute bacterial UTI.

Category II: Chronic bacterial prostatitis (CBP) which is caused by chronic bacterial infection of the prostate with or without prostatitis symptoms and usually with recurrent UTIs caused by the same bacterial strain.

Category III: Chronic prostatitis/chronic pelvic pain syndrome which is characterized by chronic pelvic pain symptoms and possibly voiding symptoms in the absence of UTI.

Category IV: Asymptomatic inflammatory prostatitis (AIP) which is characterized by prostate inflammation in the absence of genitourinary tract symptoms.

Prostatitis is the most common urological diagnosis in men <50 years of age and is the third most common diagnosis among those 50 years of age. Approximately 10% of men have chronic prostatitis-like symptoms; of these men, 60% have sought medical help. The lifetime probability of a man receiving a diagnosis of prostatitis is 125%, and prostatitis accounts for 25% of men's office visits for genitourinary complaints. Reported rates of prostatitis are similar in North America, Europe, and Asia. In addition to discomfort, prostatitis syndromes are responsible for substantial physical and emotional distress and financial costs.[1]

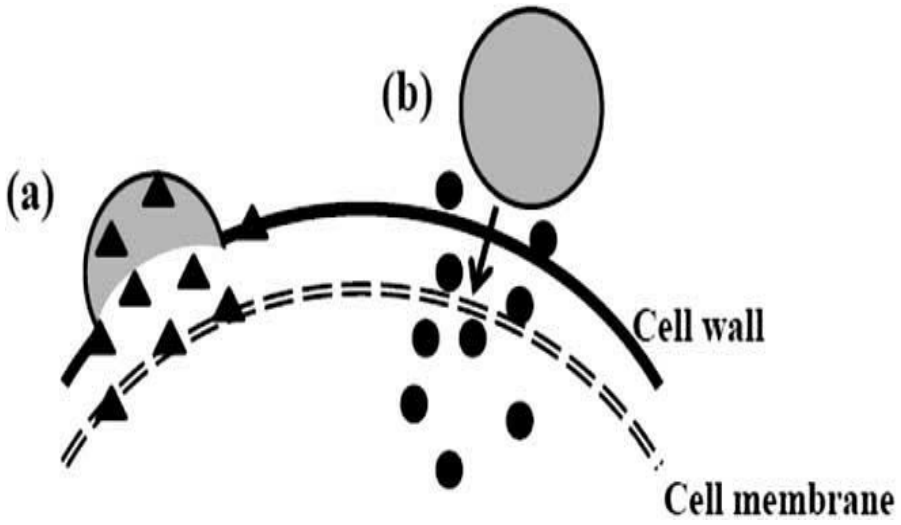


Fig.1. Mechanisms of nanoparticle-based antimicrobial drug delivery to microorganisms: (a) nanoparticles fuse with microbial cell wall or membrane and release the carried drugs within the cell wall or membrane; (b) nanoparticles bind to cell wall and serve as a drug depot to continuously release drug molecules, which will diffuse into the interior of the microorganisms.[9]

Over the last few decades, the applications of nanotechnology in medicine have been extensively explored in many medical areas, especially in drug delivery. Dimensions of nanoparticles may range from 1-1000 nm It is currently accepted that the diameter of nanoparticles for prostatitis should be in the range of 10-300 nm, so they may easily penetrate and accumulate within the prostate gland (Fig. 1.) .they provide large surface to mass ratio, high reactivity and unique interactions with biological systems

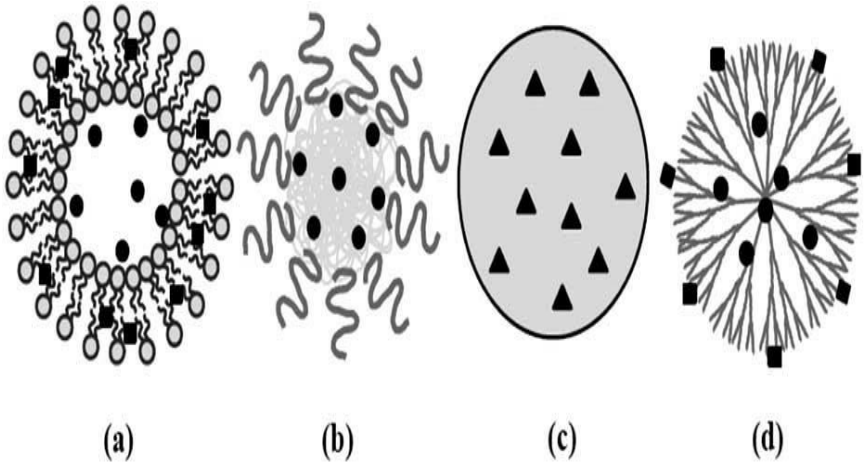


Fig.2.Schematic illustrations of four nanoparticle platforms for antimicrobial drug delivery proposed for prostatitis: (a) liposome, (b) polymeric nanoparticle, (c) solid lipid nanoparticle, and (d) dendrimer. Black circles represent hydrophobic drugs; black squares represent hydrophilic drugs; and black triangles represent either hydrophobic or hydrophilic drugs.

Moreover, drug-loaded nanoparticles can enter host cells through endocytosis and then release drug payloads to treat microbes-induced intracellular infections as prostatitis. As listed in Fig. 2. , A few types of nanoparticles including liposomes, polymeric nanoparticles, solid lipid nanoparticles and dendrimers have been widely investigated as antimicrobial drug delivery platforms

Active Targeting to Prostate

On a molecular level, the interaction between the targeting moiety and the targeted epitope is highly affected by the binding affinity and selectivity of the targeting unit and by the capacity of the targeted receptors .First, the number of cell-surface receptors and their availability dictate the number of targeting molecules that will eventually bind specifically to the Prostate. Once the surface receptor is saturated by the carrier systems.[2,5]

Passive Targeting to prostate

Passive targeting results from the Enhanced Permeability and Retention (EPR), allowing nanoparticles to diffuse into the prostate tissue. Naturally, smaller particles will more readily penetrate into the same. The accumulation of the diffusing NPs in the tissue, on the other hand, is attributed to the lack of lymphatic drainage which also characterizes the tumor environment. Although; it is known that this EPR effect is not sufficient for efficient accumulation of low-molecular-weight drugs at the target site.[2,5]

Non-covalent Ligand Conjugation Approaches:

The most widely investigated non covalent approaches include

1. Adsorption of the ligand/Ab to the surface of the NPs.

2. Biotin-Avidin complexes

Adsorption is not an ideal conjugation method, as competitive displacement of the ligand/ Ab by blood components could occur upon intravenous injection of the NPs and infinite dilution in the blood Biotin-avidin complexes exhibit a very strong noncovalent natural bond, however, as avidin is derived from bacterial streptavidin or from the egg white, its potential immunogenicity limits its use in vivo . Thus, covalent binding is currently the preferred approach for antibody Conjugation.

Covalent Ligand Conjugation Approaches:

This can be achieved by various methods. We will only mention the two most commonly described linkage processes [2]

1 Amide linkage – Activation of the end groups of carboxyl terminated PLA and PLGA by a carbodiimide (such as EDC- 1-Ethyl-3-[3-dimethylaminopropyl]carbodiimide Hydrochloride) will result in an active ester intermediate that can be coupled to the amine functional groups of an antibody by carbodiimide chemistry

2 Thioether linkage – The reaction between thiol functional groups and maleimide groups is highly efficient and leads to stable thioether bonds. Such a linkage may be formed between maleimide-bearing NPs and thiolated antibodies or other thiol bearing ligands . Alternatively, thiol-surface activated NPs may also react with maleimide-activated antibodies

Other targeting strategy approaches [2,5]

1. Monoclonal Antibodies (MAb): Monoclonal antibodies are macromolecules widely used as Targeting ligands because of their immediate and variable availability and their high affinity and specificity to molecular targets. These targeting ligands usually possess a molecular weight of about 150kDa and exhibit high binding affinities of the drawbacks in the use of MAbs as therapeutic or targeting agents is the concern of their immunogenicity.
2. Affibodies : An affibody is a small, stable 58-amino acid Z-domain scaffold, derived from the IgG binding domain of staphylococcal protein A. Its binding pocket is composed of 13 amino acids, and it is able to bind to a variety of targets, depending the randomization of the amino acids. As opposed to IgGs, its small size (~6-15kDa) enables infected tissue and cell penetration. Affibodies possess a high receptor affinity that mimics the active portion of the Fab' region of the corresponding antibody. Their short half life makes them good candidates as tumor imaging probes but not ideal tools for targeting direct drug conjugates, where long circulation times are required.

3. Aptamers: Aptamers are an emerging class of targeting ligands which, like antibodies, may also serve as biological drugs in the treatment of various diseases. The advent of monoclonal antibodies over the past decade and the use of peptide hormones, growth factors and cytokines have been continuously providing a spectrum of protein-based ligands needed for a selective targeting of tumor-associated antigen and cancer biomarkers. However, issues concerning the size, cost and immunogenicity of such protein-based ligands have led to the search for alternative ligand families. Aptamers, are short single-stranded synthetic nucleic-acid oligomers, DNA or RNA oligonucleotides (ssDNA, ssRNA), that can form complex three-dimensional structures with the ability to bind to the internalized surface markers and target molecules with high affinity and specificity.
4. Folic Acid Receptor Targeting: Folate receptor (FR) is another common targeted epitope in drug delivery research. It is a glycosyl phosphatidyl inositol anchored glycoprotein (38–40 kDa). Notably, folate receptor (FR) is highly expressed inbacterial infections such as prostatitis. The use of its correspondence, the vitamin folic acid (Folate, FA), as a highly efficient targeting moiety is already long acclaimed due to its small size, high binding affinity for folic acid receptor (FR) (Kd =10-10 M), lack of immunogenicity, high stability, ready availability and low cost . Moreover, normal tissues lack FR expression, avoiding any possible deleterious effects on normal cells. Folic acid is reported to be taken up by FRs by a hypothesized process known as potocytosis.
5. Prostate Specific Membrane Antigen (PSMA)-Targeting NPs: The main methodology reported for PSMA targeted drug delivery has been based on the employment of aptamer-conjugated nanocarriers. However, several works have also employed anti- PSMA antibodies for the targeted delivery of magnetic iron oxide NPs and dendrimers.

(Fig.3.)

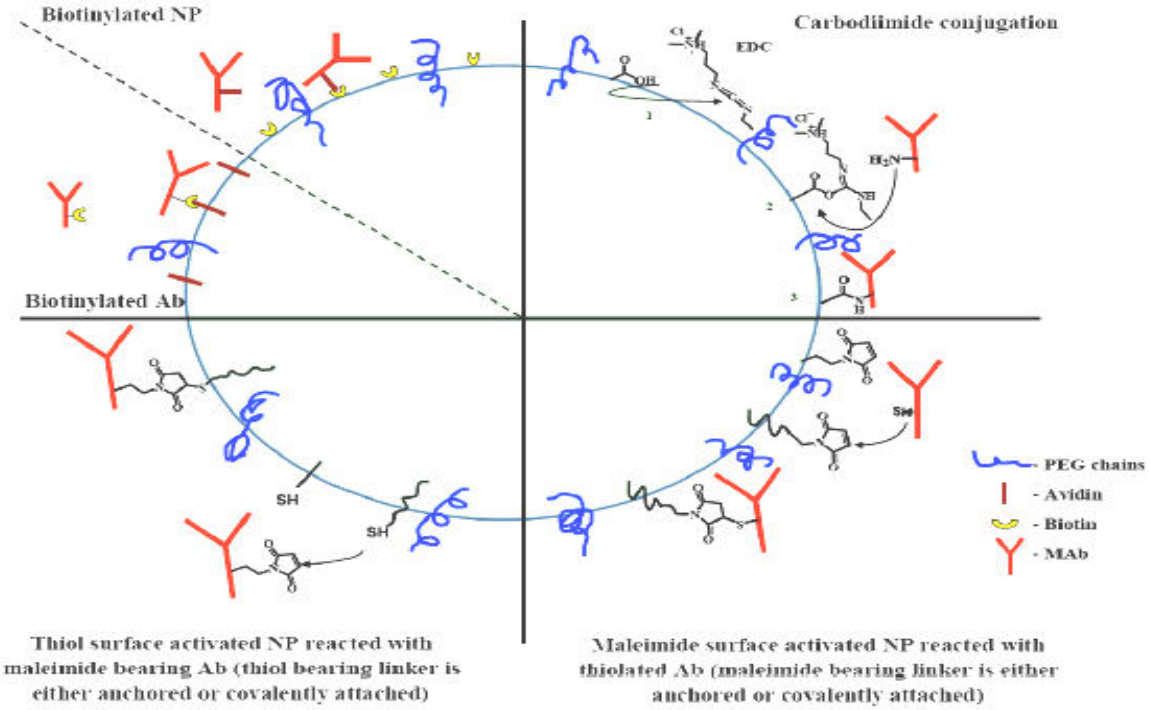


Fig.3. Schematic illustration of ligand conjugation approaches to polymeric nanoparticle surface. Other targeting strategy approaches [2,5]

Animal Models for Prostatitis

- The prostatitis infection can be induced by prostatic introduction of *E. coli* present a model of acute (in 100%) prostatitis which is self-limiting and chronic (in 50%) whole prostate and ventral lobe prostatic inflammation with high percentage of eliminated animals due to their death or sterile prostate; evidence that an androgen deprivation might decrease bacterial growth and improve course of chronic bacterial prostatitis.
- Strain, lobe-specific and age-dependent prostatitis. 17b-estradiol given to male adults increases incidence and severity of spontaneous prostatitis. (Harmone) Long-term (10 days) stress stimuli (starvation, low surrounding temperature, and small cage) induce prostatic inflammation (Stress) .
- Transurethral ethanol/dinitrobenzene sulfonic acid-mediated mucosal injury resulted in acute prostatitis that is peaked between 24 and 48 h (Irritant).
- Both 9 week oral administration of soy been extract mixture and 11 week soy-free diet were able to induce LL/DL prostatitis in 80% of rat males that may suggest for role of the estrogen/ androgen balance in initiating prostate inflammation (Diet).
- Partial mechanical obstruction of the urethra induces prostatic lymphocytic infiltration and interstitial edema, being most prominent on day 3 that might be due to intraprostatic urinary reflux (Mechanical). The Table 1. Represents various rodent models of prostate inflammation.[7,8]

Table 1. Rodent models of prostate inflammation[1]

Model	Species and strain	Inflamed site (s)
1. Spontaneous	Rat: Wistar, Lewis, Copenhagen	LL and VL
	Mouse: NOD	NA
2. Infection	Rat: Wistar, Sprague–Dawley,	VL, LL, DL
	Mouse: C3H/HeJ and C3H/HeOuJ	NA
3. Immune Prostate Ag-induced	Rat: Wistar, Lewis, Copenhagen	Male sex accessory glands, DL, LL and VL
	Mouse: C57BL/6 and NOD	NA
4. Hormone 17b-estradiol	Rat: Wistar, Lewis	LL, LL/DL and VL
	Mouse: LuRKO	NA
5. Miscellaneous Stress	Rat: Sprague–Dawley	DL, LL<VL
Irritant	Rat: Sprague–Dawley	VP
Diet	Rat: Sprague–Dawley	LL, DL
Mechanical	Rat: Wistar	VL

Abbreviations: AL, DL, LL, VL, anterior, dorsal, lateral, ventral (coagulating gland) lobes of prostate, respectively, NOD- nonobese diabetic, LuRKO - testosterone-treated LH receptor knockout.

Conclusions

Estimation of the advantages or limitations of these models is difficult because subsequent studies using these models were not carried out. Polymeric NPs would be the best candidate to target these models by various strategic approaches and significantly treat the conditions of prostatitis. A better understanding of the intracellular trafficking and final biofate of the targeted NPs might turn out to be of great influence on treatment outcomes. Such knowledge might significantly to a clever design of organelle-specific NPs. Indeed, prostatitis targeting is a highly challenging and extremely difficult task .

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