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Nano-technology for targeted drug delivery to combat antibiotic resistance

Abhinay Sharma, Deepak Kumar Arya, Meenakshi Dua,
Gursharan Singh Chhatwal & Atul Kumar Johri[†]
[†]*School of Life Sciences, Jawaharlal Nehru University, New Delhi, India*

Several microbes have evolved clinically significant resistance against almost every available antibiotic. Yet the development of new classes of antibiotics has lagged far behind our growing need. Frequent and suboptimal use of antibiotics particularly in developing countries aggravated the problem by increasing the rate of resistance. Therefore, developing new and multidimensional strategies to combat microbial infections is warranted. These include i) modification of existing antibiotics, ii) searching new and novel antibiotics, iii) development and improvement of antibiotics carrier system to reduce amount and frequency of antibiotic doses, iv) development of targeted antibiotic delivery systems. Here, the authors discuss trends and development of nano-materials and alternative antimicrobials to solve the problem of antibiotic resistance.

1. Problem of resistance and new antimicrobials: a brief update

Recently published reports have raised concerns that antibacterial drug development is too slow to address the threat of rapidly increasing antibiotic resistance among important bacterial pathogens [1,2]. Clinicians are facing shortage in the availability of alternative therapeutic options like analogs of already known compounds and new agents belonging to completely new classes of antibiotics. Ongoing research in this direction has been reviewed recently. In case of gram-negative bacterial pathogens, research is focused on old antibiotics (cephalosporins, carbapenems, β-lactamase inhibitors, monobactams, aminoglycosides, polymyxin analogs, and tetracycline) and completely new antibacterial classes (boron-containing antibacterial protein synthesis inhibitors, bis-indoles, outer membrane synthesis inhibitors, antibiotics targeting novel sites of the 50S ribosomal subunit and antimicrobial peptides) [3]. Likewise for gram-positive bacterial pathogens, research is going on old antimicrobials [quinolone, β-lactam, oxazolidinone, diaminopyrimidine, macrolide, pleuromutilin, aminoglycoside, ansamycin, FabI inhibitor, glycopeptide, metallic ion, streptogramin, tetracycline, vancomycin, dalbavancin and hybrid (oxazolidinone/quinolone and rifamycin/fluoroquinolone)] and completely new antibacterial classes (WAP 8294A2, PZ-601, ME1036, NXL101, friulimicin B, oritavancin, telavancin, ceftobiprole medocaril, ceftaroline fosamil, tomopenem, hLF1-11, lactoferrin, telactoferrin-α) with new target or new mechanism of action. But it will take long time for these drugs to reach the market because they are in the early stages of development [1,4,5]. Therefore, until these new/modified antimicrobials are available for clinicians, infection control policies and optimization in the

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use of already existing molecules remain the most effective approaches to reduce the spread of resistance and preserve the activity of antibiotics.

2. Nano-materials to combat antibiotic resistance

Although conventional antibiotics have several disadvantages like i) evolution of resistance with time, ii) low therapeutic index, iii) cytotoxicity and side effects, iv) non-specific mode of action and v) inconvenient route of administration, but these problems can be solved to some extent using different antimicrobial delivery systems involving nano-technology which refers to the design, production and application of nano-sized materials (1–100 nm). Their unique physical and chemical properties (small size, high surface-to-volume ratio and amenable for surface modification) may be exploited as vehicles to carry various therapeutic or diagnostic agents to surpass most physiological barriers and gain access to biologic molecules and intended targets. High surface-to-volume ratio allows nano-materials for increased potential to interact with pathogens and membranes. Thus, they can be potentially used for medical applications including targeted drug delivery, gene therapy and cell labeling [6]. Different types of nano-materials and alternative antimicrobials (organic and inorganic nano-materials, liposomes, biomolecules like polysaccharides, lipids, proteins/peptides and virus capsids) with medical applications have been summarized elsewhere that can help to combat antibiotic resistance [7-10]. Nano-materials tagged with antibiotics facilitate increased concentration of antibiotics at the site of infection and enhance the binding of antibiotics to bacteria. Likewise, combining nano-particles with antimicrobial peptides and essential oils generates genuine synergy against bacterial resistance [11]. Here, we describe the use of different types of nano-materials on the basis of their physio-chemical properties to facilitate targeted antimicrobial delivery and to combat the problem of antibiotic resistance.

2.1 Chitosan
Chitosan is a natural polysaccharide biopolymer derived from chitin. Being polycationic in nature, it favors the interaction of negatively charged microbial cell walls and cytoplasmic membranes, resulting in decreased osmotic stability, membrane disruption and eventual leakage of intracellular elements [12-14]. In addition, chitosan is able to enter the nuclei of bacteria and fungi and inhibit mRNA and protein synthesis by binding to microbial DNA [13]. Nano-scaled chitosan that has a higher surface-to-volume ratio, resulting in higher surface charge density, leads to increased affinity to bacteria and fungi and greater antimicrobial activity. Findings of previously published reports have encouraged using this nano-material for antibiotic encapsulation and efficient delivery [6,12-17].

2.2 Liposomes
Liposomes are spherical vesicles consisting of one or more phospholipid bilayers surrounding a water space. The diameter of the liposome varies from 0.02 to 10 µm. Vesicle formulations are usually based on natural and synthetic phospholipids and cholesterol. The structure may also possess lipoproteins [18]. The physicochemical properties of liposomes can be modified by changing the types of lipids: the composition and proportions of lipids in the liposomal formulation; the size of the liposome; the charge of the liposomal surface: positive, negative, or neutral; pH sensitivity; temperature sensitivity; the fluidity of the liposomal membrane: rigid and fluid liposomes. Regarding the variety of liposomal formulations, the vesicles are universal carriers for both hydrophilic and hydrophobic compounds. The size of the liposomal vesicles significantly influences drug distribution. Large (> 1 µm) MLV (Multilamellar Vesicles) formulations are usually not used as antibiotic carriers, but SUVs (Small Unilamellar Vesicles) of ~ 100 nm exhibited high efficacy in the eradication of bacterial pathogens [19].

Encapsulation of the antibiotics in lipid vesicles is a good solution for designing the required pharmacokinetic and pharmacodynamic properties [20-23]. This process may improve pharmacokinetics and biodistribution, decreased toxicity, enhanced activity against intracellular pathogens, target selectivity, enhanced activity of antibiotics against extracellular pathogens, in particular to overcome antibiotic resistance. More details about advantages and recent applications about liposome can be found elsewhere [19]. Antibiotic delivery (β-lactams, ampicillin, cephalosporins, macrolides, aminoglycosides, and fluoroquinolones) to enhance microbial killing, facilitated by nano-sized vehicles/liposomes have been reported recently.

2.3 Inorganic nano-materials
Inorganic nano-materials are either in use for centuries or under development as antimicrobials. Noble metals (like silver, gold, platinum, and palladium), carbon-based materials (carbon nano-fibers and different kinds of carbon nano-tubes), semiconducting materials (CdSe, CdS, ZnS, TiO_2, PbS, InP, Si/SiO_2), magnetic materials (Fe_3O_4, Co, $CoFe_2O_4$, FePt, CoPt and their composites) and lanthanide materials (Gd_2O_3, Eu_2O_3) are some of the important inorganic nano-materials used as antimicrobials as well as antibiotic delivery system; and have been described previously [7-9].

2.4 Silver
Silver has been used for centuries for the treatment of burns and wounds to prevent infection. The exact mechanism remains unknown, but it has been proposed that due to the smaller size of silver and silver ions (< 10 nm), they are able to penetrate bacterial cell walls and membranes via interaction with sulfur-containing proteins or thiol groups [24]. Once inside the cell, Ag/Ag^+ targets and damages bacterial DNA and respiratory enzymes, leading to loss of the cell's replicating abilities and ultimately cell death [14]. The small size and large

Table 1. Nano-carriers for antimicrobial drug delivery.

Type of nano-carrier	Composition	Encapsulated antibiotics	Target	Ref.
Liposomes	Liposome coated with chitosome	Rifampicin	Respiratory infections	[49]
	LAMB	Amphotericin B	Fungal pathogens	[50]
	PG, PC, and Chol	Streptomycin	*Mycobacterium avium*	[51]
	DPPC and Chol	Ciprofloxacin	*Salmonella dubli*	[52]
		Polymyxin B	*Pseudomonas aeruginosa*	[53]
	EPC, DCP, and Chol	Vancomycin or Teicoplanin	MRSA	[54]
	DPPC, Chol, and DC-Chol	Benzyl penicillin	*Staphylococcus aureus*	[55]
	SPC and Chol	Ampicillin	*Micrococcus luteus, Salmonella typhimurium*	[56]
	HSPC, Chol, and DSPG	Amikacin	Gram-negative bacteria	[57]
Solid lipid nano-particles	SA, SPC, and STC	Tobramycin	*Pseudomonas aeruginosa*	[58]
	SA	Rifampicin, Isoniazid, Pyrazinamide	*Mycobacterium tuberculosis*	[59]
	GPS	Econazole nitrate	Fungi	[60]
	SA, SPC, and STC	Ciprofloxacin hydrochloride	Bacteria and mycoplasma	[61]
Solid nano-particles	PLA	Linezolid	MRSA	[62]
	PCL	Amphotericin B	*Leishmania donovani*	[63]
	PLGA	Rifampin and Azithromycin	*Chlamydia trachomatis, Chlamydia pneumoniae*	[64]
		Tobramycin	Respiratory infections	[65]
		Clarithromycin	*Escherichia coli, Haemophilus influenzae, Salmonella typhi, Staphylococcus aureus, Streptococcus pneumoniae*	[66]
	PIHCA	Ampicillin	*Listeria monocytogenes*	[67]
	PAA	N-methylthiolated β-lactams	MRSA	[68]
		Penicillin	MRSA	[69]
	GPAA	N-sec-butylthio β-lactam, Ciprofloxacin	*Staphylococcus aureus, Bacillus anthracis*	[70]
Dendrimers	PAMAM	Silver salts	*Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli*	[71]
		Sulfamethoxazole	*Escherichia coli*	[72]
		Nadifloxacin and Prulifloxacin	*Escherichia coli*	[41]
		Azithromycin	*Chlamydia trachomatis*	[73]
	PLCP	Artemether	*Plasmodium falciparum*	[74]

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Chol: Cholesterol; DC-Chol: Dimethylammonium ethane carbamoyl cholesterol; DCP: Diacetylphosphate; DSPG: Distearoyl phosphatidylglycerol; DPPC: 1,2-Dipalmitoylphosphatidylcholine; EPC: Egg PC; GPAA: Glycosylated polyacrylate; GPS: Glycerol palmitostearate; HSPC: Hydrogenated soybean phosphatidyl choline; LAMB: Liposome amphotericin B; MRSA: Methicillin-resistant *Staphylococcus aureus*; PAA: Polyacrylate; PAMAM: Polyamidoamine; PC: Phosphatidyl choline; PCL: Poly ε-carprolactone; PG: Phosphatidyl glycerol; PIHCA: Polyisohexylcyanoacrylate; PLA: Poly lactic acid; PLCP: Pegylated lysine based copolymeric dendrimer; PLGA: Poly lactide-co-glycolide; SA: Stearic acid; SPC: Soybean phosphatidyl choline; STC: Sodium taurocholate.

surface area of silver nano-particles (AgNPs) makes them effective against a variety of pathogens [13,14,24-28]. AgNPs have also been found to augment the efficacy of other antibiotics, like the activity of penicillin G, amoxicillin, erythromycin, clindamycin and vancomycin increased against *S. aureus* and *E. coli* when mixed with AgNPs [26]. Microbes are also less likely to develop resistance against silver and AgNPs, as their broad range of targets would require multiple and simultaneous compensatory mutations. As a result, silver can be used to arrest bacterial resistance to antibiotics and enhance their efficacy [14].

2.5 Copper

Copper is utilized for its antifungal and antibacterial activity but the mechanism remains unknown. The use of CuO nano-particles (CuO-NPs) as a novel antimicrobial agent has recently been investigated. When compared to AgNPs, CuO-NPs were shown to be less effective against *E. coli* and methicillin-resistant *S. aureus* but more effective against *B. subtilis*, which may be due to copper's greater interaction with amine and carboxyl groups on the cell surface of this pathogen [27,29]. Other metals (like zinc, titanium and magnesium) are also used and reported to be potential antimicrobials/carriers which have been described elsewhere [6].

2.6 Carbon nano-tubes

Carbon nano-tubes (CNTs) are emerging as a new family of nano-vectors for the delivery of different types of therapeutic molecules given their capacity to interact with
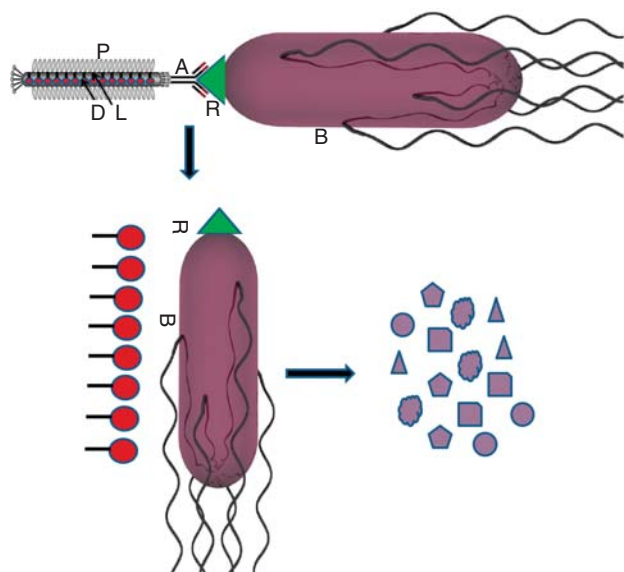
Figure 1. Schematic representation of targeted drug delivery by using filamentous phage to kill pathogenic bacteria colonized in host. Receptor and antibody specificity can be exploited for targeted delivery. Genetically engineered filamentous phage loaded with drug molecules inside its protein coat and displaying antibody on its tip can burst to release drug molecules when it binds with its complementary receptors. The released drug molecules attack pathogenic bacteria and kill it specifically. Here 'A' stands for antibody; 'B' for bacteria; 'P' for protein coat; 'D' for drug/antibiotic; 'L' for chemical linker and 'R' for receptor.

macromolecules such as proteins, antibiotics and oligosaccharides [30-32]. Covalent modification by the organic functionalization of end groups and side walls of f-CNTs allows for a dramatic increase of the solubility of functionalized carbon nano-tubes in a range of solvents, including water [33]. Water-soluble carbon nano-tubes interact with mammalian cells, leading to their cytoplasmic translocation [32]. These properties led us to believe that f-CNTs may be an effective vehicle for oral administration of AmB [30].

2.7 Biodegradable polymeric nano-particles
Biodegradable polymeric nano-particles came into picture for the first time in 1980s and have been extensively investigated for enhanced intracellular drug delivery [34]. Structural stability in biologic fluids and under harsh conditions, precisely tunable properties (e.g., size, zeta-potentials, and drug release profiles) [35] and facile and versatile surface functionalization for conjugating drugs and targeting ligands [36] are various advantages of polymeric nano-particles. Majority of polymeric nano-particles prepared with linear polymers are either nano-capsules or solid nano-spheres [37]. Other kind of polymeric nano-particles are amphiphilic block copolymers which are self-assembled micellar NPs

with the drug encapsulating hydrophobic core and the hydrophilic corona shielding the core from opsonization and degradation [38].

2.8 Dendrimers
Dendrimers are hyperbranched polymers with precise nano-architecture and low polydispersity, which are synthesized in a layer-by-layer fashion around a core unit, resulting in a high level control of size, branching points (drug conjugation capability), and surface functionality [39]. The highly branched nature of dendrimers provides enormous surface area to size ratios that generate great reactivity to microorganisms *in vivo* [35]. The highly dense surface of functional groups allows the synthesis of dendrimers with specific and high binding affinities to a wide variety of viral and bacterial receptors [40]. Both hydrophobic and hydrophilic drugs can be loaded/conjugated/adsorbed inside empty internal cavities in the core and on the multivalent surfaces of dendrimers respectively [41]. Polymeric nano-particles have been explored to deliver various antimicrobial agents and greatly enhanced therapeutic efficacy in treating many types of infectious diseases has been reported and described in **Table 1**.

2.9 Targeted drug-carrying phages
Targeted drug-carrying phages are a new class of nano-medicines that combines biologic and chemical components into a modular nano-metric drug delivery system (bio-conjugated delivery system). The core of the system is filamentous phage particles which are produced in the bacterial host *Escherichia coli*. Target specificity is provided by a targeting moiety, usually an antibody that is displayed on the tip of the phage particle. A large drug payload is chemically conjugated to the protein coat of the phage via a chemically or genetically engineered linker that provides for controlled release of the drug after the particle homed to the target cell (**Figure 1**) [42]. Hepatitis B virus (HBV) vaccine is one of the best examples of bio-conjugated nano-particles delivery system. These are bionano-capsules (BNCs) consisting of hepatitis B virus (HBV) surface antigen (HBsAg) (approximately 50-nm hollow particles) displaying a human hepatocyte-recognizing molecule (pre-S1 peptide) [43].

Despite its potential, there are various limitations of nano-carriers, which include size, charge, purity, solubility of contents, stability, antigenicity, and biocompatibility. Lower tolerance for variability in these parameters can lead to increased costs of synthesis and manufacture. The specificity of delivery of nano-carriers to target tissues can be passive or active. Passive targeting has been exemplified in recently published reports which described the use of enhanced permeability and retention (EPR) effect to deliver tumor-selective macromolecular drugs [44]. Active targeting of nano-carriers is dependent on receptor-ligand interactions. Sometimes activation of nano-carrier drug

delivery is dependent on cellular activity (pH change or oxidative burst).

3. Alternative strategies to cope up antibiotics resistance

New alternative strategies have been proposed recently to solve the problem of scarcity of novel antibiotics. One of the alternative approaches is to target functions essential for infection, such as virulence factors required to cause host damage and disease. This approach has several potential advantages including expanding the repertoire of bacterial targets, preserving the host endogenous microbiome, and exerting less selective pressure, which may result in decreased resistance. Recently published reviews have described this approach in detail [45,46]. Another strategy is focused on natural antimicrobials, known as host defense peptides or antimicrobial peptides, which defend host organisms against microbes but most have modest direct antibiotic activity. Following this approach, enhanced variants have been developed using straightforward design and optimization strategies and are being tested clinically. Recently published review described advanced computer-assisted design strategies that address the difficult problem of relating primary sequence to peptide structure, and is delivering more potent, cost-effective, broad-spectrum peptides as potential next-generation antibiotics [47,48].

4. Conclusion

This is high time to address the problem of antibiotic resistance and to work on alternative strategies to find out the solutions. Here, we suggested some of them very briefly. Nano-technology and nano-medicines are emerging fields that may be utilized for antibiotic delivery. It will not only increase therapeutic index but also reduce the problem of non-specific cytotoxicity as well as antibiotic resistance. It is essential to develop cost effective nano-materials and improve their capacity to carry antibiotics and deliver more efficiently. More focused studies are also required to develop targeted antibiotic delivery systems like bacteriophages. Other alternative strategies are also worthy to look for searching novel compound and antibiotics which can target virulence functioning of microbes. Antimicrobial peptides, lipopeptides and other natural compounds should also be screened and already existing compounds should be engineered to enhance their antimicrobial efficiency. Following these multiple approaches is a prerequisite to find the solution for antibiotic resistance.

Declaration of interest

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Affiliation

Abhinay Sharma[1], Deepak Kumar Arya[1], Meenakshi Dua[3], Gursharan Singh Chhatwal[2] & Atul Kumar Johri[†1]
[†]Author for correspondence
[1]School of Life Sciences, Jawaharlal Nehru University, New Delhi, 110067, India
Tel: +91 11 26704511;
Fax: +911126742558;
E-mail: akjohri14@yahoo.com
[2]Helmholtz Centre for Infection Research, Department of Medical Microbiology, Inhoffenstraße 7, 38124 Braunschweig, Germany
[3]School of Environmental Sciences, Jawaharlal Nehru University, New Delhi, 110067, India

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