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Review Article

Prevention and Therapeutics of Pneumococcal Infections and Diseases by Using Nanomedicine

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Abstract

Pneumonia is one of the leading causes of death worldwide declared by the World Health Organization (WHO), particularly among aging and pediatric population and with millions of bacterial pneumonia cases each year. The significantly increasing incidence of bacterial pneumonia in both children and the elderly is found due to decreased immune function. In recent years, the problem of drug resistance in bacterial pneumonia has become increasingly serious due to the misuse of antibiotics. Bacterial pneumonia is a serious infectious disease, and its current therapeutic strategies have led to the development of multi-drug resistant bacteria. Finding drugs that are alternatives to traditional antibiotics would be an effective solution to this challenge. Currently, nanomedicines can change improve the targeting and penetration of antibiotics, and the drug size thus improving bioavailability and reducing systemic toxic effects. For enhancing vaccine-induced antigen immunogenicity and specific immune responses with widely using for infectious disease prevention, tumor immunotherapy, etc. nanomedicine can be served as vaccine delivery vectors and adjuvants. Meanwhile, nanomaterials, like lipid nanoparticles (LNPs), polymeric NPs, and exosomes, can act as delivery systems for targeted drug distribution, controlled release, and effective treatment.

In conclusion, the disadvantages of the exosomes could be compensated by other types of NPs to achieve the targets.

Keywords: *Nanomedicine; Nanoparticles; Pneumococcal Infections; Pneumococcal Diseases; Elderly; Aging Population; Pneumococcal Vaccines; Pneumococcal Vaccination; COVID-19 Vaccines; COVID-19 Vaccination; SARS-CoV-2*

Abbreviations

AgNPs: Silver Nanoparticles; AuNPs: Gold Nanoparticles; COVID-19: Coronavirus Disease 2019; HBV: Hepatitis B Virus; HIV: Human Immuno-Deficiency Virus; PEG: Polyethylene Glycol; PLA: Poly (Lactic Acid); PLGA: Poly (Lactide-Co-Glycolic) Acid; RBD: Receptor-Binding Domain; VLP: Virus-Like Particles; S: *Streptococcus*; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; siRNA: Small Interfering RNA; MNPs: Magnetic Nanoparticles; VLP: Virus-Like Particles; WHO: World Health Organization

Currently, nanomedicines can change improve the targeting and penetration of antibiotics, and the drug size thus improving bioavailability and reducing systemic toxic effects [1]. World Health Organization (WHO) declared that pneumonia is one of the leading

causes of death worldwide, particularly among children and aging population with millions of pneumonia cases each year, particularly bacterial pneumonia. The significantly increasing incidence of bacterial pneumonia in both the elderly and children is found due to decreased immune function [1]. *Streptococcus pneumoniae, Staphylococcus aureus, Escherichia coli* and *Legionella pneumophila* are the common causative organisms. In recent years, the problem of drug resistance in bacterial pneumonia has become increasingly serious due to the misuse of antibiotics [1]. Bacterial pneumonia is a serious infectious disease, and its current therapeutic strategies have led to the development of multi-drug resistant bacteria. Finding drugs that are alternatives to traditional antibiotics would be an effective solution to this challenge [2]. Diverse biomedicine applications is enabled by various NPs characteristics. Nanomaterials can serve as adjuvants and vaccine delivery vectors to enhance vaccine-induced specific immune responses and antigen immunogenicity, and are widely used for infectious disease prevention, tumor immunotherapy, etc. Meanwhile, nanomaterials, like lipid nanoparticles (LNPs), polymeric NPs, and exosomes, can act as delivery systems for targeted drug distribution, controlled release, and effective treatment [3]. High-sensitivity detection of specific targets and real-time monitoring of disease progression can be provided by surface-functional-groups fine-tuning, such as quantum dots (QDs) and nanomaterials-like magnetic NPs for biomedical-imaging using [4,5]. Additionally, integration into protective equipment like masks, gloves, and disinfectants, serving as wound dressings to prevent infections can be performed through nanomedicine with antibacterial and antiviral properties. Here, we delineated the characteristics of each NP variant (Table 1) [6], particularly focusing on their application in the prevention, treatment, and detection/diagnosis of infections and diseases (Figure 1) [6].

Types of NPs	Composition	Advantages	Disadvantages	Examples of applications
Lipid NPs	Lipids are commonly used in liposomes, including lecithin, triglycerides, triglycerides of palm stearate, and fatty acids	Flexible surface modification; strong drug loading capacity, and high biocompatibility.	Limited stability under certain environmental conditions; limited control of drug release rate; costly preparation, potential toxicity at high dosages	Targeting lung therapy COVID-19
				Making mRNA vaccines against Zika virus infection
				Vitamin lipid nanoparticles can be used to treat septicaemia caused by drug-resistant bacteria
				Glycyrrhetinic acid-lipid framework nanocarriers improve drug loading efficiency of anti-hepatocellular carcinoma drugs
Metal NPs	Metal and metal oxide NPs, including silver, gold, CuO, SiO_2, TiO_2 and various other metal oxides	Unique shape, size, structure, and local-field enhancement action	Potential toxicity; limited stability with aggregation and morphological changes; environmental pollution concerns; limited degradation *in vivo*	Intravaginal zinc oxide tetrapod NPs against genital herpes
				AgNPs on H1N1 inhibit influenza A virus
				Delivery of antiviral siRNA with AuNPs inhibits dengue virus infection
				Cuprous oxide NPs against Hepatitis C Virus

Carbon-based NPs	Carbon nanotubes	Large specific surface area and hollow structure; increasing application capability by surface modification; good chemical and physical stability	Pulmonary toxicity; complex preparation steps; varying diameters, lengths, structures	Multiwalled carbon nanotubes for the detection of zooplankton in water
	Graphene	Excellent mechanical properties; high strength and flexibility; high specific surface area	Limitation in stability; aggregation in aqueous solution affects stabilization and release; potential biotoxicity issues	Sulfonated MNPs functionalized destroy herpes simplex virus type 1.
	Fullerenes	Antioxidant properties; stable structure; surface modification to obtain multiple properties	Relatively low load capacity; low solubility in water	Fullerene derivatives inhibit HIV by complexing with HIV protease.
				C60-β-cyclodextrin conjugate improves nuclear transport of doxorubicin
Polymeric NPs	Natural hydrophilic polymers and synthetic hydrophobic polymers	Good drug loading capacity and controlled release capabilities; easy synthesis and regulation	Long-term toxicity from body accumulation; potentially toxic degradation products; complex preparation and functionalization	Porous PLA and PLGA NPs for pulmonary delivery of HBV vaccine
				(PEG-b-PLA) NPs improve protein affinity for delivered drugs
Protein NPs	VLP	High structural stability and resistance to degradation; immunocompatibility; biomimetic properties	Inefficient protein delivery *in vivo*; insufficient immunogenicity, requiring adjuvants and multiple injections for vaccination; complex preparation process	Novel virus-like particle vaccine encoding the circumsporozoite protein of plasmodium falciparum is Immunogenic.
				Engineered VLPs for efficient delivery of therapeutic proteins.
	Proteins	Good biocompatibility and biodegradability; multifunctionality through surface modification.	Complex preparation and functionalization; high production costs; limited drug loading capacity	Dual-sensitive antibacterial peptide nanoparticles prevent dental caries.
				Development of spike RBD ferritin proteins vaccine against SARS-CoV-2 infection in ferrets
Exosomes	Classification according to source	Excellent biocompatibility; targetability	Poor experimental reproducibility; characterization difficulties; heterogeneity; difficulty in production standardization, and harsh storage conditions	Recombinant SARS-CoV-2 receptor-binding structural domain-modified exosomes as inhalable COVID-19 vaccines.

Table 1: *Demonstrating the advantages and disadvantages of existing NPs in drug delivery and vaccines [12].*

Abbreviations: VLP: Virus-Like Particles; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; HIV: Human Immuno-Deficiency Virus; siRNA: Small Interfering RNA; AgNPs: Silver Nanoparticles; AuNPs: Gold Nanoparticles; MNPs: Magnetic Nanoparticles; HBV: Hepatitis B Virus; PLGA: Poly (Lactide-Co-Glycolic) Acid; PEG: Polyethylene Glycol; PLA: Poly (Lactic Acid); RBD: Receptor-Binding Domain.

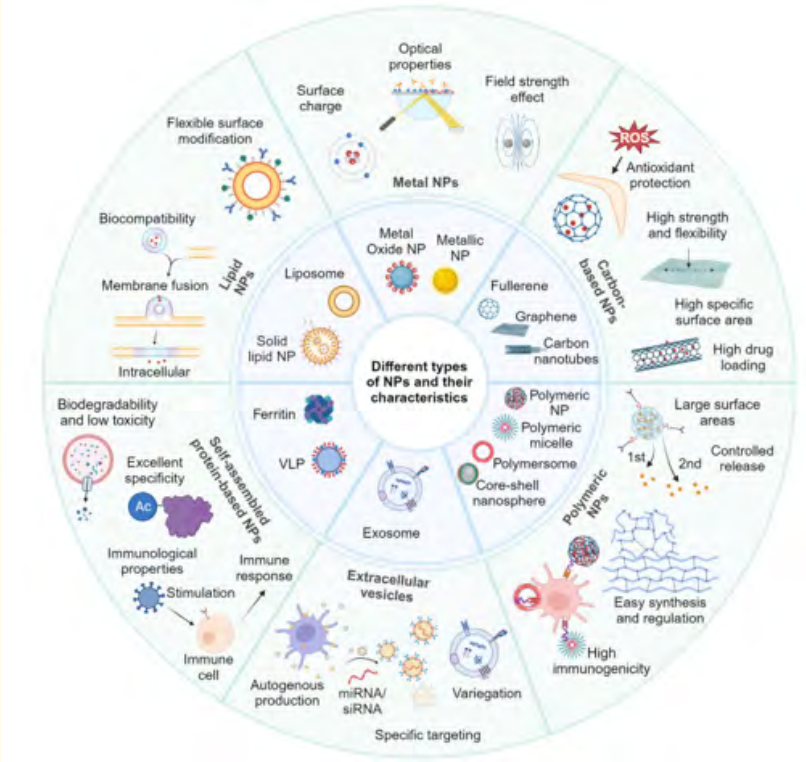

Figure 1: *Demonstrating the characteristics of the six common nanomaterials. Exhibiting good biocompatibility and flexible surface modification capabilities demonstrated in lipid NPS with composing of lipids such as phospholipids. Metal NPs, including metals (such as gold, silver, copper) and their metal oxides, possess excellent optical, electronic, and magnetic properties, enabling applications in biological imaging, PTT, and sensing [7]. Carbon-based nanomaterials, including CNTs, graphene, and fullerenes, not only have a large surface area and high drug loading capacity but also exhibit high strength and chemical stability, allowing resistance to oxidative environments [8]. Displaying diverse structures and properties due to composing of polymer materials are found in polymer NPs [9]. Ferritin family proteins and VLPs, self-assembled NPs, possess good biodegradability in the case of the former and can mimic viral stimuli to initiate immune responses in the case of the latter [10]. Exosomes, a type of small vesicles secreted by cells, carry abundant proteins, nucleic acids, and signaling molecules, playing vital roles in information transfer and regulation [11]. These and exosomes have broad applications in the biomedical and nanotechnology fields, including drug delivery, molecular imaging, biosensing, tissue engineering, and disease diagnosis.*

Conclusion

In conclusion, several NPs have different advantages and disadvantages, compared to each others. For example, exosomes have excellent biocompatibility and targetability; but they have difficulty in standardized production; poor experimental reproducibility; characterization difficulties; heterogeneity; harsh storage conditions [12]. The disadvantages of the exosomes could be compensated by other types of NPs to achieve the targets.

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