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Bacterial Nanocarriers for Site-Specific Drug Delivery: Harnessing Microorganisms for Precision Medicine

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Abstract:

Bacterial nanocarriers represent a promising approach for site-specific drug delivery, offering precise targeting and controlled release of therapeutic agents. This review provides an overview of the application of bacterial nanocarriers in precision medicine, focusing on their potential to target specific sites within the body for enhanced therapeutic outcomes. The key characteristics of bacterial nanocarriers, including size and shape, surface modifications for targeting and stealth capabilities, payload capacity, loading efficiency, stability, and biocompatibility, are discussed. This review explores various types of bacterial nanocarriers, including bacterial outer membrane vesicles (OMVs), bacterial spores, engineered bacteria, and other bacteria-based nanocarriers, highlighting their unique properties and applications. The mechanisms of site-specific drug delivery, including passive targeting via the enhanced permeability and retention (EPR) effect, active targeting using ligands and receptors, and tumor microenvironment-specific activation, are examined to elucidate the precise delivery mechanisms employed by bacterial nanocarriers. Furthermore, this review discusses the diverse applications of bacterial nanocarriers in precision medicine, including cancer therapy, infectious diseases, and chronic diseases, emphasizing their potential for targeted delivery of chemotherapeutic agents, immunotherapy, antibiotics, vaccines, and sustained release formulations. Challenges such as immunogenicity, manufacturing scalability, regulatory hurdles, and approval processes are addressed, along with future directions and emerging technologies in the field. Overall, bacterial nanocarriers hold immense promise as versatile platforms for site-specific drug delivery, paving the way for advancements in precision medicine and personalized therapeutics.

Keywords: bacterial nanocarriers, precision medicine, drug delivery, targeted therapy, cancer, nanotechnology.

I. Introduction

Precision medicine is a medical approach that takes into account individual variability in genes, environment, and lifestyle for each person. It recognizes that each individual is unique, and thus, treatments should be tailored to specific characteristics rather than adopting a one-size-fits-all approach[1]. Precision medicine aims to improve treatment outcomes, minimize side effects, and optimize healthcare resources by targeting therapies to patients who are most likely to benefit from them.Precision medicine encompasses various fields, including genomics, proteomics, metabolomics, and other omics disciplines, along with clinical and health data analysis[2]. This has led to advancements in disease prevention, diagnosis, and

treatment across various medical specialties, including oncology, cardiology, neurology, and infectious disease[3].

The foundation of precision medicine lies in understanding the molecular mechanisms underlying diseases and identifying biomarkers that can predict disease susceptibility, progression, and response to treatment. With the advent of high-throughput technologies and bioinformatics tools, researchers can analyse vast amounts of biological data to elucidate disease pathways and develop targeted therapies[4].Precision medicine has the potential to revolutionize healthcare by shifting from a reactive approach to a proactive and personalized approach. By identifying individuals at risk of disease and providing targeted interventions, precision medicine aims to improve patient outcomes, reduce healthcare costs, and enhance overall population health[5].Site-specific drug delivery is a crucial aspect of precision medicine that aims to deliver therapeutic agents directly to the site of action within the body while minimizing systemic exposure and off-target effects. Traditional drug delivery systems often result in low drug concentrations at the target site, leading to suboptimal efficacy and increased risk of adverse reactions[6].Site-specific drug delivery offers several advantages over conventional systemic administration. It allows for higher drug concentrations at the desired site, leading to enhanced therapeutic efficacy and reduced dosage requirements. By minimizing exposure to healthy tissues, site-specific drug delivery can also reduce side effects and improve patient compliance with treatment regimens[7].Site-specific drug delivery is particularly important in the treatment of localized diseases, such as cancer, inflammatory disorders, and infections. In cancer therapy, for example, delivering chemotherapy directly to the tumor site can increase the likelihood of tumor regression while minimizing damage to surrounding healthy tissues[8]. Similarly, targeted drug delivery can improve the efficacy of antimicrobial agents in treating infections by delivering high concentrations of drugs to the site of infection.Various approaches have been developed for site-specific drug delivery, including passive and active targeting strategies. Passive targeting relies on the physiological properties of tissues, such as the enhanced permeability and retention (EPR) effect observed in tumors, to deliver drugs selectively to the target site. Active targeting involves the use of ligands, antibodies, or other targeting moieties to facilitate specific interactions with receptors or antigens expressed on target cells, further enhancing drug delivery efficiency[9].

Bacterial nanocarriers represent a promising platform for site-specific drug delivery, harnessing the unique properties of bacteria to deliver therapeutic agents to specific tissues or cells within the body. Bacteria possess several inherent advantages as drug delivery vehicles, including their small size, ability to penetrate biological barriers, and capacity for targeted localization.Bacterial nanocarriers can be engineered to express specific surface molecules or proteins that facilitate targeting to particular tissues or cells[10]. Moreover, bacteria can be genetically modified to produce and release therapeutic agents directly at the site of action, providing sustained drug release and minimizing systemic exposure.Several types of bacterial nanocarriers, including bacterial outer membrane vesicles (OMVs), bacterial spores, and engineered bacteria, have been explored for drug delivery applications[11]. OMVs are naturally produced by bacteria and can be loaded with therapeutic cargo for targeted delivery to host cells. Bacterial spores, such as those produced by Clostridium species, have been investigated as vehicles for delivering drugs or imaging agents specifically to hypoxic regions

within solid tumors. Engineered bacteria can be designed to target specific tissues or cells and deliver therapeutic payloads in response to environmental cues or stimuli[12].

The aim of this review article is to provide a comprehensive overview of bacterial nanocarriers for site-specific drug delivery and their potential applications in precision medicine. This review covers the characteristics of bacterial nanocarriers, including size, shape, surface modifications, payload capacity, and stability. The mechanisms of site-specific drug delivery by bacterial nanocarriers, including passive and active targeting strategies, are also discussed[13].Furthermore, this review highlights the applications of bacterial nanocarriers in precision medicine, with a focus on cancer therapy, infectious diseases, and chronic conditions. The challenges and limitations associated with bacterial nanocarriers, such as immunogenicity, manufacturing scalability, and regulatory considerations, are discussed. Finally, this review provides insights into future directions and emerging technologies in the field of bacterial nanocarriers for site-specific drug delivery.

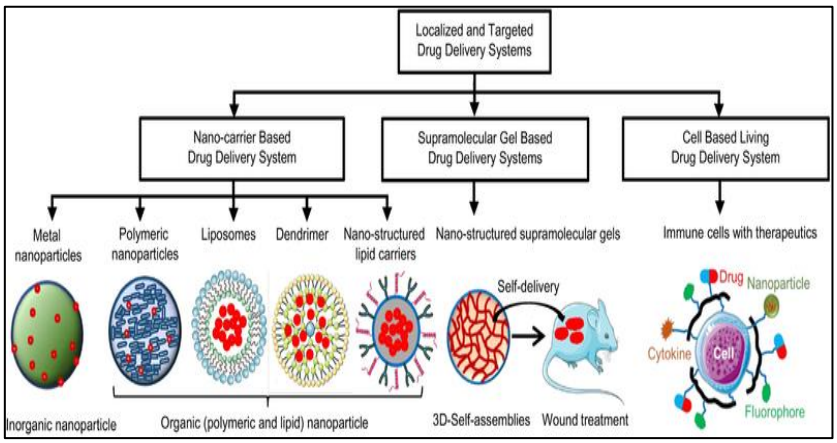

Figure 1: Diverse Carrier-Based Systems for Localized and Targeted Drug Delivery

II. Characteristics of the Bacterial Nanocarriers

A. Size and shape considerations

The size and shape of bacterial nanocarriers play a crucial role in determining their behavior and efficacy as drug delivery vehicles. Bacterial nanocarriers are typically nanosized particles ranging from a few nanometres to several hundred nanometres in diameter[14]. The small size of bacterial nanocarriers enables them to penetrate biological barriers, such as cell membranes and tissue barriers, and reach target sites within the body more efficiently.The shape of bacterial nanocarriers can also influence their biodistribution, cellular uptake, and targeting capabilities[15]. Various shapes, including spherical, rod-shaped, and filamentous, have been explored for use as bacterial nanocarriers. For example, spherical nanoparticles may exhibit prolonged circulation times in the bloodstream and enhanced cellular uptake, while rod-shaped or filamentous particles may improve tumor penetration and retention[16].

Furthermore, the aspect ratio of bacterial nanocarriers, defined as the ratio of their length to width, can impact their interactions with biological systems. High aspect ratio particles, such as nanorods or nanowires, may exhibit enhanced cellular uptake and internalization compared to spherical particles due to their elongated shape. However, excessively high aspect ratios

may also increase the risk of cytotoxicity or immune recognition, highlighting the importance of optimizing the shape and aspect ratio of bacterial nanocarriers for specific applications[17].

B. Surface modifications for targeting and stealth capabilities

Surface modifications of bacterial nanocarriers play a crucial role in enhancing their targeting specificity and stealth capabilities while minimizing immune recognition and clearance[5]. The surface of bacterial nanocarriers can be modified with various functional groups, polymers, peptides, or antibodies to facilitate specific interactions with target cells or tissues[18].Targeting ligands, such as antibodies, peptides, or small molecules, can be conjugated to the surface of bacterial nanocarriers to recognize and bind to specific receptors or antigens expressed on target cells[6]. This enables precise targeting of therapeutic agents to diseased tissues while minimizing off-target effects on healthy cells. For example, antibodies targeting overexpressed receptors on cancer cells can be conjugated to bacterial nanocarriers to achieve tumor-specific drug delivery[2].In addition to targeting ligands, surface modifications can also impart stealth properties to bacterial nanocarriers to evade immune detection and clearance[19]. PEGylation, the conjugation of polyethylene glycol (PEG) chains to the surface of nanoparticles, is a commonly used strategy to increase the circulation half-life of bacterial nanocarriers by reducing opsonization and phagocytosis by the reticuloendothelial system (RES). PEGylation creates a hydrophilic barrier around bacterial nanocarriers, preventing protein adsorption and recognition by immune cells[20].

C. Payload capacity and loading efficiency

The payload capacity and loading efficiency of bacterial nanocarriers are critical factors that determine their therapeutic efficacy and practical utility as drug delivery vehicles[13]. The payload capacity refers to the maximum amount of therapeutic agent that can be loaded onto or encapsulated within bacterial nanocarriers, while the loading efficiency reflects the percentage of drug encapsulated relative to the total capacity of the nanocarrier[21].Bacterial nanocarriers offer several advantages for drug loading and encapsulation, including their large surface area, internal compartmentalization, and potential for genetic engineering. Therapeutic agents can be loaded onto bacterial nanocarriers through physical adsorption, chemical conjugation, encapsulation within vesicles or compartments, or genetic expression and secretion by engineered bacteria[22].The payload capacity of bacterial nanocarriers can vary depending on factors such as the size, shape, and composition of the nanocarrier, as well as the physicochemical properties of the therapeutic agent. For example, small-molecule drugs may be loaded at higher concentrations than larger biologics or nucleic acids due to differences in molecular size and solubility[8].Loading efficiency is influenced by various parameters, including the method of drug loading, the affinity between the drug and nanocarrier, and the stability of the drug-nanocarrier complex. Optimizing loading efficiency is essential to maximize the therapeutic payload delivered to the target site while minimizing waste and ensuring cost-effectiveness[23].

D. Stability and biocompatibility

The stability and biocompatibility of bacterial nanocarriers are critical considerations for their safe and effective use in drug delivery applications[3]. Bacterial nanocarriers must maintain their structural integrity and drug-loading capacity during storage, transportation, and administration to ensure reliable and consistent therapeutic outcomes[24].Stability encompasses various aspects, including physical stability (e.g., aggregation, sedimentation, or degradation), chemical stability (e.g., drug degradation or release), and biological stability (e.g., susceptibility to enzymatic degradation or immune recognition)[2,4]. Strategies to enhance the stability of bacterial nanocarriers include surface modifications, encapsulation within protective matrices or coatings, and formulation optimization[25].Biocompatibility refers to the compatibility of bacterial nanocarriers with biological systems, including cells, tissues, and the immune system. Bacterial nanocarriers should exhibit minimal cytotoxicity, immunogenicity, or inflammatory responses to ensure their safety and tolerability in vivo[11]. Biocompatibility can be influenced by factors such as the composition, surface chemistry, and degradation products of bacterial nanocarriers, as well as their interactions with host cells and tissues[6].Various in vitro and in vivo assays, including cell viability assays, cytokine profiling, histological analysis, and pharmacokinetic studies, are used to assess the stability and biocompatibility of bacterial nanocarriers. Preclinical safety evaluations are essential for identifying potential adverse effects and guiding the design and optimization of bacterial nanocarriers for clinical translation[26].

III. Types of Bacterial Nanocarriers

A. Bacterial outer membrane vesicles (OMVs)

OMVs are nanoscale spherical structures naturally released by gram-negative bacteria as part of their normal growth and metabolism[5]. OMVs are composed of outer membrane lipids, proteins, and various cargo molecules, including toxins, enzymes, nucleic acids, and cell wall components. These vesicles range in size from 20 to 300 nanometers and are enriched in outer membrane proteins and lipopolysaccharides[27].OMVs have garnered significant interest as potential drug delivery vehicles due to their biocompatibility, stability, and ability to encapsulate and protect cargo molecules from degradation. OMVs can be engineered to display specific antigens or ligands on their surface, allowing for targeted delivery to specific cell types or tissues[2,9]. Additionally, OMVs can be loaded with therapeutic agents, such as drugs, vaccines, or nucleic acids, for targeted delivery to diseased tissues or cells.The unique properties of OMVs make them promising candidates for various biomedical applications, including vaccine delivery, cancer therapy, and infectious disease treatment[28]. OMV-based vaccines have been developed against bacterial pathogens, such as *Neisseria meningitidis* and Vibrio cholerae, by loading OMVs with antigenic proteins or polysaccharides derived from target pathogens. These vaccines have shown promising efficacy in preclinical and clinical studies, providing protection against bacterial infections.In addition to their use in vaccine delivery, OMVs have been explored for targeted drug delivery in cancer therapy[3,8]. Engineered OMVs can be loaded with chemotherapeutic agents or nucleic acids and functionalized with targeting ligands to specifically deliver drugs to tumor cells while minimizing off-target effects on healthy tissues. Moreover, OMVs can be used as adjuvants to enhance the immune response and efficacy of cancer immunotherapies[29].

B. Bacterial spores

Bacterial spores are dormant, highly resistant structures formed by certain bacterial species in response to adverse environmental conditions. Spores are characterized by their tough outer coat, which protects the bacterial genome and cellular contents from desiccation, heat, radiation, and chemical damage. Bacterial spores can remain viable for extended periods, making them attractive candidates for drug delivery and biotechnological applications[19].Bacterial spores have been explored as natural carriers for drug delivery due to their unique properties, including their small size (1-2 micrometres), stability, and capacity for payload encapsulation[30]. Spores can be genetically engineered to produce and release therapeutic agents in response to specific stimuli or environmental cues, such as pH, temperature, or the presence of target molecules.One of the most extensively studied bacterial spores for drug delivery is the spore-forming bacterium *Clostridium difficile*[12]. Engineered *C. difficile* spores have been used as targeted delivery vehicles for cancer therapy by exploiting the hypoxic microenvironment of solid tumors. These spores are engineered to germinate selectively within the tumor microenvironment and release therapeutic payloads, such as cytotoxic drugs or imaging agents, specifically within the tumor tissue[31].

C. Engineered bacteria

Engineered bacteria are genetically modified microbial strains designed to deliver therapeutic agents or perform specific functions within the body for biomedical applications. Engineered bacteria offer unique advantages as drug delivery vehicles, including their inherent targeting capabilities, capacity for self-replication, and potential for on-demand drug production[23].

One of the most widely studied engineered bacteria for drug delivery is *Escherichia coli* (*E. coli*), a common gram-negative bacterium[17]. Engineered *E. coli* strains have been designed to express and release therapeutic proteins, peptides, enzymes, or nucleic acids in response to specific environmental cues or stimuli. These bacteria can be administered orally, intravenously, or directly to target tissues to deliver therapeutic payloads to desired sites within the body.Engineered bacteria can be programmed to target specific cell types or tissues by modifying their surface proteins or introducing targeting ligands or peptides[32]. Moreover, bacteria can be engineered to express and release therapeutic agents in a controlled manner, providing sustained drug release and minimizing systemic toxicity[22].Several strategies have been explored to enhance the safety and efficacy of engineered bacteria for drug delivery, including the use of containment mechanisms to prevent bacterial replication in vivo, inducible expression systems for controlled drug release, and genetic circuitry to enable bacterial communication and coordination within microbial consortia.Engineered bacteria hold great promise for a wide range of biomedical applications, including cancer therapy, infectious disease treatment, and metabolic engineering[17]. However, challenges remain in the development of engineered bacteria, including issues related to biosafety, immunogenicity, and regulatory approval. Ongoing research efforts continue to address these challenges and advance the clinical translation of engineered bacteria for precision medicine[33].

D. Other bacterial-based nanocarriers

In addition to OMVs, bacterial spores, and engineered bacteria, other bacteria-based nanocarriers have been explored for drug delivery applications[20]. These include engineered bacterial ghosts, bacterial cell-derived nanoparticles, and bacterial-derived extracellular vesicles.Engineered bacterial ghosts are empty bacterial cell envelopes derived from gram-negative bacteria that have been genetically modified to remove their genetic material. These empty cell envelopes retain the surface structures and membrane components of the original bacteria and can be loaded with therapeutic agents for targeted drug delivery[34]. Bacterial ghosts offer advantages such as biocompatibility, immunogenicity, and potential for surface functionalization.Bacterial cell-derived nanoparticles are nanosized particles derived from intact bacterial cells through various physical or chemical methods, such as sonication, homogenization, or extrusion[18]. These nanoparticles retain the structural and functional properties of the original bacteria and can be loaded with drugs, proteins, or nucleic acids for targeted delivery. Bacterial cell-derived nanoparticles offer advantages such as biocompatibility, stability, and potential for surface modification[35].

IV. Mechanisms of Site-Specific Drug Delivery

A. Passive targeting via the enhanced permeability and retention (EPR) effect

Passive targeting exploits the unique physiological characteristics of diseased tissues, such as tumors, to achieve site-specific drug delivery. The enhanced permeability and retention (EPR) effect is a phenomenon commonly observed in solid tumors, wherein leaky blood vessels and impaired lymphatic drainage lead to the accumulation of macromolecules and nanoparticles within the tumor microenvironment[31].Solid tumors are characterized by abnormal vasculature with discontinuous endothelial cell junctions and fenestrations, allowing for increased vascular permeability[36]. This abnormal vascular architecture, coupled with poor lymphatic drainage, results in the retention of macromolecules and nanoparticles within the tumor interstitium. As a result, systemically administered drugs or nanoparticles can preferentially accumulate in tumor tissues, providing a passive targeting mechanism for site-specific drug delivery[25].The EPR effect is primarily exploited for the delivery of nanoparticle-based therapeutics, such as liposomes, polymeric micelles, and nanoparticles, which are too large to penetrate normal blood vessels but can extravasate and accumulate in tumor tissues through leaky tumor vasculature[36]. Once they accumulate within the tumor interstitium, these nanoparticles can release their payload of therapeutic agents, such as chemotherapy drugs, nucleic acids, or imaging agents, to exert their therapeutic effects.The passive targeting approach offers several advantages for site-specific drug delivery, including simplicity, noninvasiveness, and broad applicability to various types of solid tumors[21]. However, the efficacy of passive targeting via the EPR effect can be highly variable depending on the tumor type, size, and stage, as well as individual patient factors. Moreover, the heterogeneity of the tumor vasculature and the presence of stromal components within the tumor microenvironment can limit the extent of nanoparticle accumulation and hinder drug delivery efficiency[37].

B. Active targeting using ligands and receptors

Active targeting involves specific interactions between targeting ligands, such as antibodies, peptides, aptamers, or small molecules, conjugated to the surface of drug carriers, and receptors or antigens overexpressed on the surface of target cells or tissues[20]. This targeted approach enhances the specificity and efficiency of drug delivery while minimizing off-target effects on healthy tissues.Targeting ligands can be selected or engineered to recognize specific biomarkers associated with diseased tissues, such as cancer cells, inflammatory cells, or pathogenic microorganisms[38]. These ligands bind to their cognate receptors with high affinity and specificity, facilitating the selective uptake of drug carriers into target cells via receptor-mediated endocytosis or other internalization mechanisms[19].Various types of targeting ligands have been employed for active targeting, including monoclonal antibodies, antibody fragments (e.g., Fab or scFv), peptides (e.g., cell-penetrating peptides or tumor-homing peptides), aptamers (e.g., nucleic acid-based ligands), and small molecules (e.g., folate or transferrin)[7]. These ligands can be conjugated to the surface of drug carriers, such as liposomes, nanoparticles, or polymer micelles, using chemical, biological, or physical coupling methods.Active targeting using ligands and receptors offers several advantages over passive targeting, including enhanced specificity, reduced systemic toxicity, and improved therapeutic efficacy[39]. By directing drug carriers specifically to diseased tissues or cells, active targeting can increase the local concentration of therapeutic agents, improve cellular uptake, and overcome barriers to drug delivery, such as the blood–brain barrier or multidrug resistance mechanisms[3].Moreover, active targeting can be combined with other strategies, such as stimuli-responsive drug release or synergistic combination therapy, to further enhance the therapeutic outcomes of targeted drug delivery. For example, stimuli-responsive drug carriers can release their payload selectively in response to specific environmental cues or physiological conditions within the target tissue, further improving drug efficacy and reducing off-target effects[40].

C. Tumor microenvironment-specific activation

Tumor microenvironment-specific activation is a strategy for site-specific drug delivery that exploits the unique biochemical and physiological characteristics of the tumor microenvironment to trigger the release or activation of therapeutic agents within tumor tissues[21]. The tumor microenvironment is a complex and dynamic ecosystem composed of tumor cells, stromal cells, immune cells, blood vessels, and extracellular matrix components[41].

The tumor microenvironment exhibits several distinctive features that can be targeted for site-specific drug delivery, including acidic pH, hypoxia, elevated levels of enzymes and biomarkers, and aberrant expression of receptors or signalling pathways. By harnessing these tumor-specific cues, drug delivery systems can be designed to respond selectively to the tumor microenvironment and release therapeutic agents specifically within tumor tissues while sparing healthy tissues[19].One approach for tumor microenvironment-specific activation involves the use of stimuli-responsive drug carriers that undergo structural changes or release their payload in response to specific stimuli or environmental cues present within the tumor microenvironment[16]. For example, pH-sensitive nanoparticles can be designed to

release their cargo in response to the acidic pH of tumor tissues, leading to localized drug delivery and enhanced therapeutic efficacy[42].

Another approach involves the use of prodrugs or inactive drug precursors that are activated selectively within the tumor microenvironment by tumor-specific enzymes or metabolic pathways[8]. Upon activation, these prodrugs are converted into their active form, exerting their therapeutic effects specifically within tumor tissues while minimizing systemic toxicity.Furthermore, nanotechnology-based platforms, such as liposomes, nanoparticles, or polymer micelles, can be functionalized with targeting ligands or antibodies to achieve tumor-specific accumulation and cellular uptake[43]. These targeted drug delivery systems can exploit tumor-specific biomarkers or receptors for selective binding and internalization into tumor cells, enhancing drug delivery efficiency and therapeutic outcomes.Tumor microenvironment-specific activation strategies offer several advantages for site-specific drug delivery, including enhanced specificity, reduced systemic toxicity, and improved therapeutic efficacy[18]. By targeting tumor-specific cues and mechanisms, these strategies can overcome barriers to drug delivery and enhance the accumulation and retention of therapeutic agents within tumor tissues[44].

Table 1. Antitumour drug-loaded nanocarriers for the treatment of various tumors

Nanocarrier	**Drug(s)**	**Tumor**	**Benefits**	**References**
Liposomes	Doxorubicin, Paclitaxel	Breast cancer	Controlled drug release, reduced systemic toxicity	[2]
Polymeric nanoparticles	Docetaxel, Cisplatin	Lung cancer	Enhanced drug stability, targeted delivery to lung tissue	[5]
Dendrimers	Methotrexate, Paclitaxel	Ovarian cancer	High drug loading capacity, tumor penetration	[10]
Carbon nanotubes	Cisplatin, Gemcitabine	Pancreatic cancer	Ability to penetrate deep into tumor tissue, sustained drug release	[18]
Gold nanoparticles	Cisplatin, 5-Fluorouracil	Colorectal cancer	Enhanced cellular uptake, photothermal therapy enhancement	[13]
Magnetic nanoparticles	Methotrexate, Doxorubicin	Brain tumors	Magnetic targeting, enhanced blood–brain barrier penetration	[22]
Mesoporous silica nanoparticles	Paclitaxel, Docetaxel	Prostate cancer	High surface area for drug loading, pH-responsive drug release	[29]
Nanogels	Methotrexate, Irinotecan	Gastric cancer	Stimuli-responsive drug release, prolonged circulation time	[34]

V. Applications of Bacterial Nanocarriers in Precision Medicine

A. Cancer therapy

Cancer therapy represents one of the most promising applications of bacterial nanocarriers in precision medicine, offering targeted and personalized treatment options for patients with various types of cancer. Bacterial nanocarriers hold great potential for improving the efficacy and safety of cancer therapy through targeted drug delivery, immunomodulation, and combination therapy approaches[45].

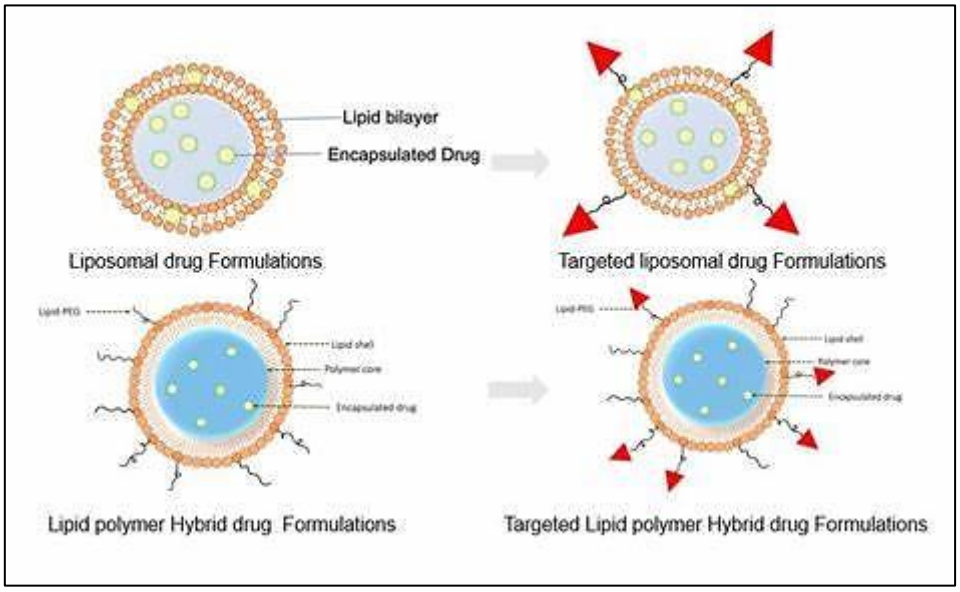

Figure 2: Nanoparticle-Based Systems for Delivering Cancer Therapeutics

Targeted delivery of chemotherapeutic agents

Chemotherapy is a cornerstone of cancer treatment, but its efficacy is often limited by systemic toxicity and off-target effects on healthy tissues. Bacterial nanocarriers can address these limitations by delivering chemotherapeutic agents selectively to tumor tissues while minimizing exposure to healthy organs[6]. By exploiting passive or active targeting mechanisms, bacterial nanocarriers can enhance the accumulation of chemotherapeutic drugs within tumors, leading to improved therapeutic outcomes and reduced side effects.Passive targeting via the enhanced permeability and retention (EPR) effect allows bacterial nanocarriers to accumulate preferentially in tumor tissues due to the leaky vasculature and impaired lymphatic drainage characteristic of solid tumors[46]. This passive targeting mechanism can be further enhanced by optimizing the size, shape, and surface properties of bacterial nanocarriers to improve their tumor penetration and retention[26].Active targeting strategies involve the conjugation of targeting ligands, such as antibodies, peptides, or small molecules, to the surface of bacterial nanocarriers to facilitate specific interactions with receptors or antigens overexpressed on tumor cells. These targeted drug delivery systems can enhance the specificity and efficiency of drug delivery to tumor tissues, resulting in improved therapeutic efficacy and reduced systemic toxicity[29].Moreover, bacterial nanocarriers can be engineered to release chemotherapeutic drugs in response to specific stimuli or environmental cues within the tumor microenvironment, such as acidic pH, hypoxia, or enzymatic activity. Stimuli-responsive drug delivery systems enable controlled and triggered

release of therapeutic agents within tumor tissues, further enhancing drug efficacy and minimizing off-target effects[47].

Immunotherapy using bacterial vectors

In addition to targeted drug delivery, bacterial nanocarriers hold promise for cancer immunotherapy by harnessing the immune system to recognize and eliminate tumor cells[5]. Bacterial vectors can be engineered to express and deliver immunomodulatory agents, such as cytokines, chemokines, or immune checkpoint inhibitors, to the tumor microenvironment, thereby enhancing the antitumour immune response and overcoming immune evasion mechanisms employed by cancer cells[48].Bacterial nanocarriers can serve as potent adjuvants for cancer vaccines, promoting antigen presentation and activation of tumor-specific immune responses. Engineered bacteria can be designed to express tumor-associated antigens or neoantigens and deliver them to antigen-presenting cells, such as dendritic cells, to stimulate T-cell-mediated immune responses against tumor cells[15]. Moreover, bacterial vectors can be modified to express immunostimulatory molecules, such as interleukins or costimulatory ligands, to enhance the activation and proliferation of antitumour immune cells within the tumor microenvironment[20].

Furthermore, bacterial nanocarriers can be engineered to modulate the tumor microenvironment and promote antitumour immune responses while inhibiting the immunosuppressive mechanisms employed by cancer cells[7]. For example, bacteria can be engineered to express enzymes that convert immunosuppressive metabolites, such as adenosine or indoleamine 2,3-dioxygenase (IDO), into immunostimulatory molecules, thereby reversing the immunosuppressive tumor microenvironment and enhancing the efficacy of cancer immunotherapy[49].

B. Infectious diseases

Bacterial nanocarriers hold promise for the treatment of infectious diseases, offering targeted delivery of antibiotics, vaccines, and immunomodulatory agents to combat microbial pathogens while minimizing systemic toxicity and antimicrobial resistance[13].

Targeted delivery of antibiotics

Antibiotic resistance poses a significant threat to global public health, necessitating the development of novel strategies for targeted and personalized antimicrobial therapy. Bacterial nanocarriers can enhance the efficacy and specificity of antibiotic delivery by targeting microbial pathogens directly to infected tissues or cells while sparing the commensal microbiota and minimizing off-target effects[50].

Bacterial nanocarriers can be engineered to encapsulate or conjugate antibiotics and deliver them selectively to sites of infection, such as bacterial biofilms, intracellular pathogens, or localized infections[10]. By exploiting passive or active targeting mechanisms, bacterial nanocarriers can enhance the accumulation of antibiotics within infected tissues, leading to improved antimicrobial efficacy and a reduced risk of resistance development.Passive targeting strategies leverage the enhanced permeability and retention (EPR) effect to deliver antibiotic-loaded bacterial nanocarriers preferentially to sites of infection, such as inflamed tissues or bacterial biofilms[6]. Active targeting approaches involve the conjugation of

targeting ligands or peptides to the surface of bacterial nanocarriers to facilitate specific interactions with microbial surface molecules or host cell receptors, enabling selective binding and internalization of antibiotic-loaded carriers into infected cells or pathogens[51].

Vaccines and immunomodulation

Bacterial nanocarriers offer promising platforms for the development of novel vaccines and immunomodulatory therapies to prevent and treat infectious diseases[13]. Engineered bacteria can be designed to express and deliver antigens or immunomodulatory molecules to the immune system, thereby stimulating protective immune responses against microbial pathogens or modulating host immune responses to enhance pathogen clearance and resolution of infection[4].Bacterial vectors can be engineered to express antigens derived from microbial pathogens and deliver them to antigen-presenting cells, such as dendritic cells, to stimulate the activation and proliferation of pathogen-specific T and B cells[52]. Moreover, bacterial nanocarriers can be modified to express adjuvants or immunostimulatory molecules that enhance the immune response to vaccination, promoting the production of protective antibodies and memory T cells against microbial pathogens.Furthermore, bacterial nanocarriers can be engineered to modulate host immune responses and promote immune-mediated clearance of microbial pathogens[2]. Engineered bacteria can express immunomodulatory molecules, such as cytokines, chemokines, or Toll-like receptor agonists, that enhance innate and adaptive immune responses against infection. Moreover, bacterial nanocarriers can be designed to target specific immune cell populations or tissues involved in host defense mechanisms, such as mucosal surfaces or lymphoid organs, to enhance the efficacy of vaccination or immunotherapy[53].

C. Chronic diseases

Bacterial nanocarriers hold potential for the treatment of chronic diseases, offering targeted delivery to specific organs or tissues affected by pathological processes while minimizing systemic toxicity and off-target effects. Moreover, bacterial nanocarriers can be designed to provide sustained release formulations that deliver therapeutic agents over an extended period, enabling long-term disease management and improved patient compliance[7].

Targeted delivery to specific organs or tissues

Chronic diseases, such as cardiovascular disease, neurodegenerative disorders, and autoimmune diseases, often require targeted drug delivery to specific organs or tissues affected by pathological processes[7]. Bacterial nanocarriers can be engineered to deliver therapeutic agents selectively to diseased tissues while sparing healthy organs, thereby enhancing therapeutic efficacy and minimizing systemic toxicity[54].Passive and active targeting strategies can be employed to achieve site-specific drug delivery in chronic diseases. Passive targeting via the enhanced permeability and retention (EPR) effect enables bacterial nanocarriers to preferentially accumulate in diseased tissues with leaky vasculature or impaired lymphatic drainage, such as inflamed or fibrotic tissues[13]. Active targeting approaches involve the conjugation of targeting ligands or peptides to the surface of bacterial nanocarriers to facilitate specific interactions with receptors or antigens overexpressed on cells or tissues affected by chronic diseases[55].Moreover, bacterial nanocarriers can be

engineered to respond to specific cues or stimuli associated with pathological processes within target tissues, such as inflammation, oxidative stress, or metabolic dysregulation, to trigger the release of therapeutic agents at the site of disease[23]. Stimuli-responsive drug delivery systems enable controlled and triggered release of drugs within diseased tissues, enhancing therapeutic efficacy while minimizing systemic exposure and off-target effects[56].

Sustained release formulations

Chronic diseases often require long-term or continuous administration of therapeutic agents to achieve optimal disease management and symptom control[21]. Bacterial nanocarriers can be designed to provide sustained release formulations that deliver drugs over an extended period, thereby reducing dosing frequency, improving patient compliance, and maintaining therapeutic concentrations of drugs within target tissues.Sustained release formulations can be achieved by encapsulating drugs within bacterial nanocarriers or modifying their surface properties to control drug release kinetics[57]. By modulating factors such as particle size, surface charge, and polymer composition, bacterial nanocarriers can be tailored to release drugs at a controlled rate, ensuring prolonged therapeutic effects while minimizing fluctuations in drug concentrations.Moreover, stimuli-responsive drug delivery systems can be employed to achieve on-demand release of therapeutic agents in response to specific cues or triggers associated with disease progression or symptom exacerbation[55]. For example, bacterial nanocarriers can be engineered to respond to changes in pH, temperature, or enzyme activity within target tissues, enabling the controlled release of drugs in response to disease-specific stimuli[57].

VI. Challenges and Future Perspectives

A. Immunogenicity and safety concerns

Immunogenicity and safety concerns represent significant challenges in the development and clinical translation of bacterial nanocarriers for precision medicine applications. Bacterial nanocarriers, including engineered bacteria and bacterial-derived vesicles, have the potential to elicit immune responses and adverse reactions in patients, which can limit their therapeutic efficacy and safety[33].

Immunogenicity of bacterial nanocarriers

Bacterial nanocarriers, particularly live bacteria or bacterial vectors, can induce immune responses in the host due to their foreign antigenicity and potential for dissemination or persistence within the body[22]. Engineered bacteria may express surface antigens or pathogen-associated molecular patterns (PAMPs) that activate innate immune cells and trigger inflammatory responses, leading to adverse effects such as fever, cytokine release syndrome, or systemic inflammation[58].Moreover, bacterial nanocarriers may elicit adaptive immune responses, including antibody production and T-cell activation, against bacterial antigens or vector components, which can impact their therapeutic efficacy and lead to immune-mediated clearance or neutralization. Preexisting immunity to bacterial vectors, acquired through prior exposure or vaccination, can also influence the immune response to bacterial nanocarriers and affect their clinical performance[59].

Safety considerations of bacterial nanocarriers

Safety concerns associated with bacterial nanocarriers include the risk of infection, systemic toxicity, and unintended off-target effects[33]. Live bacteria or bacterial vectors may pose a risk of infection or dissemination within the host, particularly in immunocompromised or susceptible individuals. Bacterial nanocarriers may also produce toxins or virulence factors that contribute to adverse effects or exacerbate underlying disease conditions[12,1].Furthermore, bacterial nanocarriers must be engineered to ensure the containment and control of their behavior within the body to minimize the risk of unintended off-target effects or environmental release. Strategies to enhance the safety of bacterial nanocarriers include genetic modifications to attenuate virulence, improve containment, or enhance biocontainment, as well as formulation optimization to reduce toxicity and immunogenicity[60].

B. Manufacturing scalability

Manufacturing scalability represents a key challenge in the production of bacterial nanocarriers for precision medicine applications. The scalable and cost-effective production of bacterial nanocarriers is essential for their widespread adoption and commercialization, but it poses technical and logistical challenges that must be overcome to meet the growing demand for precision medicine therapies[19].

Complexity of bacterial nanocarrier production

The production of bacterial nanocarriers involves multiple steps, including bacterial cultivation, genetic engineering, purification, and formulation, each of which presents challenges in terms of scalability and reproducibility[12]. Bacterial cultivation requires the optimization of culture conditions, growth media, and fermentation processes to achieve high cell densities and product yields. Genetic engineering of bacteria or bacterial vectors involves the manipulation of complex biological systems and pathways, requiring expertise in molecular biology, synthetic biology, and genetic engineering techniques[61].

Moreover, the purification of bacterial nanocarriers from culture supernatants or cell lysates can be challenging due to the presence of host cell debris, contaminants, and heterogeneous populations of nanocarriers. Purification processes must be scalable, efficient, and cost-effective to yield high-purity products suitable for clinical use[14]. The formulation of bacterial nanocarriers into stable drug delivery systems, such as liposomes, nanoparticles, or hydrogels, requires the optimization of formulation parameters and quality control measures to ensure product consistency and stability[3,8].

Scalability of production processes

Scaling up production processes for bacterial nanocarriers from the laboratory scale to the industrial scale poses technical and logistical challenges, including the optimization of bioreactor systems, the automation of culture and purification processes, and compliance with regulatory requirements for good manufacturing practices (GMPs). Bioreactor design, operation, and control must be optimized to achieve high cell densities, high product yields, and high reproducibility while minimizing process variability and contamination risks[62].

C. Future directions and emerging technologies

Future directions and emerging technologies hold promise for advancing the field of bacterial nanocarriers and unlocking new opportunities for precision medicine applications. Continued research efforts are needed to address existing challenges, explore novel strategies, and

capitalize on emerging technologies to further enhance the therapeutic potential of bacterial nanocarriers.

Advancements in genetic engineering and synthetic biology

Advances in genetic engineering and synthetic biology are driving innovations in the design and engineering of bacterial nanocarriers for precision medicine applications. Novel gene editing tools, such as CRISPR-Cas9, enable precise manipulation of bacterial genomes to engineer desired traits, functionalities, and properties in bacterial nanocarriers. Synthetic biology approaches allow for the design and construction of synthetic biological systems and pathways for programmable and customizable control of bacterial nanocarrier behavior and function[63].

Development of multifunctional and smart nanocarriers

The development of multifunctional and smart nanocarriers holds promise for enhancing the therapeutic efficacy, specificity, and responsiveness of bacterial nanocarriers in precision medicine applications[64]. Multifunctional nanocarriers can integrate multiple functionalities, such as targeting ligands, stimuli-responsive materials, imaging agents, and therapeutic payloads, into a single platform to enable synergistic effects and personalized treatment strategies. Smart nanocarriers can respond dynamically to environmental cues or stimuli within the body, such as pH, temperature, or enzyme activity, to trigger the controlled release of therapeutic agents and optimize drug delivery kinetics[65].

Integration of nanotechnology and artificial intelligence

The integration of nanotechnology and artificial intelligence (AI) offers opportunities for optimizing the design, characterization, and optimization of bacterial nanocarriers for precision medicine applications[66]. AI-driven approaches, such as machine learning, computational modelling, and data analytics, can accelerate the discovery and development of novel bacterial nanocarriers by predicting structure–function relationships, optimizing formulation parameters, and identifying candidate therapies with enhanced therapeutic properties[67]. Nanotechnology-enabled AI platforms can enable high-throughput screening, rapid prototyping, and personalized optimization of bacterial nanocarriers for specific disease targets or patient populations[68].

Translation of bacterial nanocarriers from bench to bedside

The translation of bacterial nanocarriers from bench to bedside requires collaboration and integration across multiple disciplines, including basic research, translational science, clinical medicine, regulatory affairs, and commercialization. Multidisciplinary teams of researchers, clinicians, engineers, and industry partners must work together to address technical, clinical, regulatory, and commercial challenges in the development and clinical translation of bacterial nanocarrier-based therapies. Strategic partnerships with academic institutions, biopharmaceutical companies, and government agencies can facilitate the translation of bacterial nanocarriers from early-stage research to clinical development and commercialization[66].

Conclusion

In this review, we explored the role of bacterial nanocarriers in site-specific drug delivery for precision medicine applications. We discussed the characteristics, types, mechanisms, and applications of bacterial nanocarriers, highlighting their potential to revolutionize drug delivery and therapy in various disease contexts.Bacterial nanocarriers exhibit unique properties that make them attractive candidates for precision medicine. Their small size, versatile surface modifications, high payload capacity, and inherent targeting capabilities enable precise delivery of therapeutic agents to diseased tissues while minimizing systemic exposure and off-target effects. By leveraging the biological and engineering principles of bacteria, researchers can engineer sophisticated nanocarrier platforms tailored to specific disease targets, patient populations, and clinical needs.Bacterial nanocarriers hold great promise for advancing precision medicine by enabling targeted, personalized, and efficacious drug delivery strategies for a wide range of diseases, including cancer, infectious diseases, and chronic conditions. By harnessing the unique properties of bacteria, researchers can overcome the limitations of conventional drug delivery systems and achieve unprecedented levels of precision and specificity in therapeutic interventions. The ability of bacterial nanocarriers to target specific tissues, cells, or microenvironments within the body offers significant advantages for precision medicine. These nanocarriers can deliver therapeutic agents directly to diseased tissues while sparing healthy organs, minimizing side effects, and maximizing therapeutic efficacy. Moreover, bacterial nanocarriers can be engineered to respond to disease-specific cues or stimuli, enabling on-demand drug release and tailored treatment regimens for individual patients.

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