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NANOPARTICLE MEDIATED DRUG DELIVERY SYSTEMS FOR CANCER TREATMENT

Chapter 10: Nanoparticles in Gene Delivery and Theranostics

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Abstract

Nanoparticles (NPs) are recently gaining significant attention as efficient non-viral gene delivery vehicles and theranostic multifunctional platforms to overcome the main drawbacks of gene therapy, such as enzymatic degradation, suboptimal cellular uptake, endosomal trapping, and off-target side effects. This chapter describes the basic principles of gene delivery with a focus on different types of nucleic acid cargos (plasmid DNA, mRNA, siRNA, miRNA and CRISPR/Cas9), and the comparison of viral and non-viral delivery methods. The systematic classification of NPs is presented, including lipid-based systems (liposomes, solid lipid nanoparticles, nanostructured lipid carriers), polymeric nanocarriers (chitosan, PLGA, dendrimers, Polyethyleneimine), inorganic nanoparticles (gold, silver, mesoporous silica, superparamagnetic iron oxide), and carbon-based nanomaterials (carbon nanotubes, graphene oxide, fullerenes). Special focus is given to their physicochemical properties (shape, size, surface charge, functionalization), the mechanisms of their nucleic acid encapsulation, their endocytic uptake pathways, endosomal escape, their intracellular trafficking, nuclear localization, and their stimuli-responsive release. Theranostics is explored in the context of co-delivering therapeutic genes with imaging probes (MRI, CT, fluorescence, PET/SPECT) for image-guided targeted gene silencing, combinatorial chemo-gene therapy, photothermal and photodynamic therapy, and personalised oncology. Passive (EPR effect) and active targeting, as well as pH-, redox-, enzyme, and thermo-responsive systems are critically reviewed. The safety considerations like nanotoxicology, biocompatibility, immunogenicity, biodistribution, clearance, and regulatory frameworks and ethical implications, are discussed. Translation advances and challenges in scalability and commercialization are highlighted by FDA-approved nanomedicines (e.g., Onpattro) and current clinical trials. In short, the nanotube-mediated gene delivery and theranostics is a major step forward in precision medicine for cancer and genetic disorders.





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Keywords: Nanoparticles, Theranostics, Lipid Nanoparticles, CRISPR/Cas9, Nano toxicology.

1. Introduction

Nanotechnology is the ability to manipulate materials at a scale of 1–100 nm which exhibit unique physicochemical properties including high surface-to-volume ratios, quantum effects, and tunable surface chemistry (01). In biomedicine, nanoparticles (NPs) can be used as a versatile platform for drug delivery, imaging, diagnostics and therapy (02). They resist degradation by enzymes, penetrate the cell to reach the target, and do not affect other cells, allowing precise medicine (03). Applications include cancer, infectious diseases, regenerative medicine, and neurological disorders (04). In recent years, advances are made in lipid nanoparticles (LNPs) for mRNA vaccines (e.g., COVID-19) and hybrid systems for multimodal theranostics (05).

1.1 Concept of Gene Delivery

Gene delivery involves the delivery of genetic material (nucleic acids) to the target cells to modulate gene expression, correct mutations or therapeutic effects (06). Includes both gene augmentation (e.g., introducing functional genes) and gene silencing (e.g., RNAi) as well as genome editing (e.g., CRISPR/Cas). For efficient delivery, it is necessary to shield the fragile nucleic acids from nucleases, to mediate cellular delivery and to promote endosomal escape and/or nuclear or cytoplasmic delivery (07). Safety and scalability are two important advantages that non-viral vectors such as NPs have over viral vectors (08).

1.2 Theranostics

Theranostics is a combination of therapeutics and diagnostics ("therapy + diagnostics") (09). The ability to co-encapsulate therapeutic payloads (drugs/genes) and imaging agents (fluorescent dyes, MRI contrast agents, such as iron oxide NPs, or quantum dots) is made possible by the use of nanoparticles (10). This enables the real-time monitoring of biodistribution, drug release and treatment response. It can be combined with delivery of siRNA, for instance, with gold NPs for photothermal therapy (11).

1.3 Nanoparticles in Modern Therapeutics

NPs overcome these major challenges of traditional therapies: low solubility of hydrophobic drugs, fast clearance of nucleic acids, systemic drug toxicity, and drug resistance (12). The benefits of their use are the enhanced permeability and retention (EPR) effect of tumor tissue, active targeting (ligands: antibodies, peptides, aptamers) and controlled/stimuli-responsive release (pH, redox, light) and multifunctionality (13). NPs have been used in gene therapy for protecting nucleic acids, enhancing transfection efficiency and decreasing immunogenicity. (14) The clinical milestones are LNPs for mRNA vaccines and siRNA therapies (Onpattro). NPs play a key role in bringing CRISPR-based editing to the clinic (15).





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2. The Various Ways of Gene Delivery.

2.1 The Principles of Gene Delivery

The delivery of exogenous nucleic acids into cells to induce therapeutic-level gene expression or modulation is a process of gene delivery (16).

Some core principles are:

- (1) Protection from degradation.
- (2) Transport across biological barriers (blood, extracellular matrix, cell membrane).
- (3) Internalization (endocytosis).
- (4) Endosomal escape to prevent lysosomal degradation.
- (5) Release of cargo in the cytoplasm or nucleus.
- (6) Expression/Silencing with minimal off-target effects.

NPs condense nucleic acids by electrostatic interactions (cationic NPs) or by encapsulation (17).

2.2 Types of Genetic Materials

DNA: Plasmid DNA (pDNA) or minicircle DNA for long-term gene expression (e.g., therapeutic proteins). Efficient nuclear entry is needed for larger size (~several kb) (18).

siRNA: Small interfering RNA (~21-23 nt) for gene silencing by degradation of mRNA by RISC. Used in cancer and in genetic disorders (19).

mRNA: Messenger RNA for transient protein expression (e.g., vaccines, protein replacement). Is highly sensitive to nucleases, but not nuclear entering (20).

miRNA: MicroRNAs for post-transcriptional regulation. Modulators/mimics affect several pathways (21).

CRISPR/Cas Systems: Cas9 protein + guide RNA (gRNA), or mRNA/plasmid encoding them, for precise genome editing. For minimum off-target effects, they are delivered as RNP complexes (22).

2.3 Classes of Gene Delivery Systems

Viral vectors (e.g., AAV, lentivirus, adenovirus) are highly efficient at transduction and express long term, but have potential problems (e.g., immunogenicity, insertional mutagenesis, limited cargo size, manufacturing) (23).

Non-viral systems (NPs, liposomes, polymers) are safer, less immunogenic, have greater loading capacity, are more scalable, and are re-dosable. But they are not as efficient, or as transient, as they are generally considered. NPs fill this gap by engineering including ionizable LNPs. Combining benefits of both is a hybrid approach (24).

2.4 Problems with Gene Delivery

Nuclease degradation and serum instability of nucleic acids.

Cellular Uptake: Negative charge will repel cell membranes, need cationic NPs or ligands.





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Endosomal escape: Majority of NPs are retained in endosomes, proton sponge effect and/or fusogenic lipids assist.

Off-target delivery leads to toxicity: Addressed by ligands and stimuli-responsiveness.

Toxicity/Immunogenicity: Cationic NPs have cytotoxicity potential or immunogenic potential (protein corona formation changes behaviour) (25).

3. Classification and Characteristics of Nanoparticles

3.1 Nanoparticles

The materials that have at least one dimension between 1 and 100 nm or up to 1000 nm, according to some definitions, are called nanoparticles (26). In biomedicine, they are used as carriers for encapsulating and complexing with genetic materials (27).

3.2 Physicochemical Properties Nanoparticles

Size: Optimum for EPR, circulation, and uptake is 10-200nm, smaller (<5nm) for renal clearance (28).

Shape: Spherical, Rod-like or sheet-like, effects margination, penetration and uptake (e.g. rods better for tumour penetration) (29).

Surface Charge: Cationic (condensation of nucleic acids) Neutral/PEGylated (stealth & reduced opsonisation) (30).

3.3 Nanoparticles Classification

Lipid-Based Nanoparticles (LNPs, liposomes): very efficient in encapsulating mRNA/siRNA, biocompatible. Endosomal escape is accomplished by ionizable lipids. Clinical leaders (e.g. for COVID vaccines and Patisiran) (31).

Polymeric Nanoparticles (PLGA, PEI, chitosan): biodegradable and controllable release. The cationic polymers (PEI) are highly efficient DNA/RNA condensation systems, but also toxic (32).

Metallic Nanoparticles (Gold, Silver): Photothermal properties for theranostics; surface plasmon resonance for imaging and triggered release (33).

Polymeric Micelles and Nanocapsules: Gene delivery and imaging; can be used for targeted gene delivery (34).

Silica Nanoparticles (Mesoporous silica): Pores with high loading capacity, gatekeepers for stimuli-responsive release (35).

Carbon Nanotubes and Graphene: High surface area for π - π stacking with nucleic acids; mechanical strength, biocompatibility concerns (36).

Quantum Dots: Nanocrystals of semiconductors for fluorescence imaging in theranostic; usually used in combination with other carriers (37).





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3.4 Desirable Properties of Nanoparticles for Gene Delivery

Nanoparticles possess several desirable properties that make them promising systems for gene delivery:

1. **Excellent loading efficiency and protection of nucleic acids:** Nanoparticles can efficiently load and protect nucleic acid cargos from degradation.
2. **Tunable pharmacokinetic and biodistribution properties:** Their physicochemical characteristics can be modified to regulate pharmacokinetics and biodistribution.
3. **Multifunctionality:** Nanoparticles can facilitate the **co-delivery of genes and drugs** and can also serve as platforms for **theranostic applications**.
4. **Manufacturing potential:** Nanoparticle systems offer potential for successful **large-scale manufacturing**, although their immunogenicity remains an important consideration for safety and clinical translation.
5. **Ability to overcome biological barriers and enable target customization:** Nanoparticles can be engineered to overcome biological barriers and customized for targeted delivery to specific tissues or cells (38).

4. Nanoparticles in Gene Delivery.

4.1 Nanoparticles Based on Lipid

Among the non-viral vectors, lipid-based nanoparticles (LNPs) are the most clinically advanced because of their biocompatibility, biodegradability and its ability to encapsulate both hydrophilic and hydrophobic nucleic acids (39).

Liposomes: Spherical vesicles containing an aqueous core and surrounded by phospholipid bilayers. They are efficient at encapsulating DNA, mRNA and siRNA. Lipoplexes are formed by the electrostatic interaction between cationic liposomes (such as DOTAP/DOPE) and DNA. PEGylated versions have greater circulation times (40).

Solid Lipid Nanoparticles (SLNs): Solid lipid core (triglycerides) with stabilising agent (surfactants). This allows high stability and controlled release of DNA and siRNA but is not as good as LNPs for larger DNA (41).

Nanostructured Lipid Carriers (NLCs): Second generation systems which are a mixture of solid and liquid lipids. They offer increased drug/nucleic acid loading, stability and decreased expulsion during storage, which are ideal for CRISPR components (42).

4.2 The mechanism of Gene Encapsulation and Delivery:

At acidic pH (5.5) complexation at the pH is performed with the nucleic acids and ionizable lipids (such as DLin-MC3-DMA derivatives). In the case of intravenous administration, LNPs are taken up into cells through endocytosis. (43) The proton sponge effect and fusogenic mechanisms cause the ionizable lipids to protonate in the endosome's acidic environment,





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facilitating endosomal escape and disrupting the endosomal membrane. (44) Recent advances (2025–2026) include aromatic ring modified ionizable lipids (aroLNPs) that improve the targeting of the lymph nodes and the goal of reducing off-targeting to the liver, and nitro-oleic acid integration to reduce inflammation (45).

4.3 Nanoparticles Based in Polymer

Polymeric nanoparticles provide tunable degradation, high loading and versatility for different genetic cargos (46).

Cationic, mucoadhesive polymers derived from chitin, chitosan nanoparticles form polyplexes with DNA/siRNA. They are pH sensitive and are good candidates for mucosal/oral delivery (47).

PLGA Nanoparticles: FDA approved biodegradable copolymer (poly(lactic-co-glycolic acid)). They are sustained release agents and frequently surface modified with cationic agents for complexation with nucleic acids (48).

Dendrimers: highly branched tree-like structures (such as PAMAM). They have a multivalent surface, which is ideal for high nucleic acid payload and easy functionalization. Cationic dendrimers promote Endosomal escape, but need to be detoxified (49).

Polyethyleneimine (PEI) Systems: Very efficient because of the strong DNA condensation and proton sponge effect in Endosomal escape. Linear PEI, branched PEI, and PEGylated versions are used, with high molecular weight versions being potentially toxic; PEGylation renders them safer (50).

4.4 Inorganic Nanoparticles

Inorganic nanoparticles offer distinctive optical, magnetic and structural features for dual gene delivery and imaging (51).

Silver Nanoparticles (AgNPs): Highly stable and have well-documented properties for surface functionalization applications. They provide delivery of siRNAs or DNA through thiol linkages and enable theranostics (52).

Gold Nanoparticles (AuNPs): Mainly used for antibacterial properties and also for gene delivery through ROS formation and conjugation with the surface (53).

Mesoporous Silica Nanoparticles (MSNs): High pore volume for loading nucleic acids. Controlled release is made possible by gatekeepers (54).

Magnetic Nanoparticles (e.g., SPIONs): Enable magnetic guidance and MRI tracking and gene delivery (e.g., siRNA against Survivin) (55).

4.5 Nanomaterials Based on Carbon:

Carbon Nanotubes (CNTs): Single-walled or multi-walled tubes, high aspect ratio, penetrate cells. DNA/siRNA is delivered to cell via π - π stacking or covalent functionalization (56).

Graphene Oxide (GO): 2D sheets with a large surface area for loading of nucleic acid through π - π and hydrogen bonding. Combined therapy is possible thanks to the Photothermal properties (57).





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Fullerene Derivatives (e.g., C60): Spherical cages for use in PDT and as gene carriers (58).

5. The Mechanisms of Nanoparticle-Mediated Gene Delivery

The process of NP-mediated gene delivery can be divided into several steps:

1. Cellular Uptake Pathways: Endocytosis (clathrin mediated, caveolae mediated, and micropinocytosis) is the main pathway and is affected by size, charge and shape (59).

2. Endocytosis Mechanisms: Cationic NPs bind to the negative charge of membranes. Endosomal escape is a crucial step that is accomplished by proton sponge (PEI), membrane fusion (ionizable lipids) or pore formation (60).

3. Intracellular trafficking: Cytoskeletal transport to perinuclear regions, mRNA/siRNA function in cytoplasm, DNA needs to pass into the nucleus (61).

4. Nuclear Localization: Mediated by the nuclear localization signals (NLS) peptides on NPs for plasmid DNA (62).

6. Theranostics: Concept and Applications

A combination of therapy and diagnostics, a platform that diagnoses, treats and monitors disease progression.

Diagnosis and Therapy: NPs co-load therapeutic nucleic acids with imaging agents, with real-time feedback.

MRI: SPIONs as contrast agents. Gold NPs for high attenuation

CT imaging: Fluorescence Imaging: Quantum dots or dye loaded NPs.

PET/SPECT: Radionuclides labelled with NPs, for whole body tracking (63).

7. Nanoparticles in Cancer Theranostics.

Targeted Gene Delivery: Leverages EPR and ligands (e.g., RGD, folate) for oncogene silencing (e.g., EGFR, KRAS).

Nanoparticle-Assisted Chemotherapy and Gene Therapy: Co-delivery of chemotherapeutics and siRNA to overcome resistance.

Photothermal Therapy (PTT): Gold or Graphene NPs absorb NIR light and produce heat which leads to gene release.

PHT (Photodynamic Therapy): Fullerenes or gene modulating NPs produce ROS as well (64).

8. Targeted and Stimuli-Responsive Nanoparticles

Passive Targeting (EPR Effect): Accumulation in leaky tumour vasculature (optimal 10 – 200 nm size) (65).

Active Targeting: Surface ligands (antibodies, peptides such as RGD, aptamers) for receptor mediated uptake (such as EGFR, folate receptor) (66).





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9. Safety, Toxicity and Regulatory Considerations

Safety is a fundamental consideration in the clinical success of nanoparticles (NPs) for gene delivery and theranostic systems (67). These platforms have clear benefits but also have specific physicochemical properties that bring in unique toxicity and regulatory issues (68).

9.1 Nano toxicology

Nano toxicology is the assessment of the negative impact of nanomaterials on biological systems (69). The main issues are: generation of reactive oxygen species (ROS) and oxidative stress (particularly metallic and carbon based NPs), mitochondrial dysfunction, DNA damage and inflammation (70). LNPs are typically not as toxic as other nanoparticles because they are biodegradable, and they may lead to cytokine release and complement activation at high doses (71). Long-term accumulation and cellular toxicity can occur with inorganic NPs (e.g., gold, silver) through ion leaching (72).

9.2 Immunogenicity

NPs have the ability to induce adaptive and innate immune response. LNPs can trigger anti-PEG antibodies or activate the Toll-like receptors, causing infusion reactions and decreased effectiveness when repeated (73). The mRNA cargo can be immunostimulatory in its natural form (e.g., pseudouridine). Carbon nanotubes and metallic NPs tend to induce more inflammatory response (74). Mitigation involves the use of ionizable lipids, replacement of PEG with phospholipids and fine-tuning the phospholipid composition to optimize immunogenicity (75).

10. Clinical Translation and Current Marketed Products

The clinical translation of the NP gene delivery has made significant progress with success in mRNA vaccines and RNAi therapies, but with a number of challenges remaining (76).

FDA Approved Nanoparticle Systems

There are a number of NP platforms that have been introduced to the market, mostly for drug delivery, but more and more in the field of gene application:

Onpattro (Patisiran): LNP-formulated siRNA for hereditary transthyretin-mediated amyloidosis (2018) first approved RNAi therapeutic (77).

Comirnaty and Spikevax: LNP-mRNA COVID-19 vaccines; scalable gene delivery (78).

Other significant approvals include the liposomal formulations (Doxil, Onivyde) that set the stage for the nucleic acid carriers, and Vyxeos (liposomal cytarabine/daunorubicin) (79).

Conclusion:

Nanoparticles (NPs) are emerging as extremely useful non-viral vectors capable of overcoming many of the key challenges of conventional gene therapy such as enzymatic degradation, sub-optimal cellular uptake, endosomal trapping and off-target effects. The different types of nanocarriers, including lipid based, polymeric (such as chitosan, PLGA, dendrimers, PEI), inorganic (gold, silica, iron oxide), and carbon-based nanomaterials (fullerenes, graphene oxide, carbon nanotubes), can be used to efficiently encapsulate, protect, and deliver a wide





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range of nucleic acid based cargos, including pDNA, mRNA, siRNA, miRNA and CRISPR/Cas9 components. The incorporation of advanced physicochemical tuning (size, shape, surface charge and functionalization), sophisticated trafficking mechanisms (endocytosis, endosomal escape, and nuclear localization), and stimuli-responsive release strategies (pH, redox, enzyme and thermo triggered) has now greatly improved delivery precision and therapeutic efficacy. Moreover, the theranostic nature of such platforms will open the way towards image-guided personalized oncology and therapy of genetic diseases, as such they will allow simultaneous gene delivery, imaging (MRI, CT, fluorescence, PET/SPECT) and multimodal therapy (chemo-gene, photothermal, photodynamic) to be performed. The specificity of passive (EPR effect) and active targeting approaches should be increased, but persistent problems of nanotoxicology, biocompatibility, immunogenicity, biodistribution, clearance, scalability and regulatory approval need to be addressed in a systematic manner. Onpattro is just one of the landmark approvals and the increasing pipeline of clinical trials, which are clear steps toward clinical translation. To conclude, nanotube mediated and more general nanoparticle mediated gene delivery and theranostics are a revolutionizing breakthrough in precision medicine. By virtue of a framework that is continually evolving from interdisciplinary innovation, treatments for cancer, genetic diseases, and other areas of unmet medical need could offer greater safety, efficacy, and personalization.

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