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NANOBIOTECHNOLOGY IN TARGETED DRUG DELIVERY: RECENT ADVANCES AND CHALLENGES

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Abstract:

Nanobiotechnology merges nanotechnology and biomedicine to revolutionize targeted drug delivery. Conventional therapies often face poor solubility, rapid clearance, and systemic toxicity. Nanoscale carriers, such as liposomes, polymeric nanoparticles, dendrimers, and lipid nanoparticles, overcome these limitations by enhancing solubility, protecting therapeutic molecules, and precisely controlling drug release. These advanced nanocarriers utilize passive accumulation, active targeting, or responsive triggers to deliver therapies directly to specific diseased tissues. This targeted approach has completely transformed modern treatments across oncology, gene therapy, vaccines, and neurology. Despite these breakthroughs, successful clinical translation faces significant hurdles, including biological barriers, protein corona formation, potential immunogenicity, complex manufacturing, and strict regulatory demands. Developing successful precision nanomedicines requires a deeper understanding of nanoparticle pharmacokinetics, safety profiles, and reproducible manufacturing. This review comprehensively summarizes recent advances in nanobiotechnology based targeted drug delivery, evaluating the major nanocarrier platforms, broad biomedical applications, current clinical limitations, and future perspectives toward advancing precision nanomedicine today.

Keywords: *Nanobiotechnology, Targeted Drug Delivery, Nanomedicine, Nanoparticles, Nanocarriers, Liposomes, Lipid Nanoparticles, Active Targeting, Drug Delivery, Precision Medicine.*

1. Introduction

The development of effective drug-delivery systems is a major objective of pharmaceutical and biomedical research. Conventional administration of therapeutic compounds can result in several limitations, including poor aqueous solubility, instability, rapid clearance, low bioavailability, non-specific distribution, and exposure of healthy tissues to pharmacologically active compounds. These limitations can reduce therapeutic efficacy and increase adverse effects. Nanotechnology has therefore attracted considerable interest as a strategy for improving drug delivery and therapeutic performance (1).

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Nanobiotechnology combines nanoscale engineering with biological and pharmaceutical principles to produce materials and systems capable of interacting with biological structures at molecular and cellular levels. Nanoparticles generally possess high surface-area-to-volume ratios and tunable physicochemical properties. Their size, surface charge, composition, morphology, and surface chemistry can be modified according to the intended therapeutic application. Such characteristics allow nanocarriers to encapsulate, adsorb, conjugate, or otherwise transport therapeutic molecules (2).

Nanomedicine has developed particularly rapidly in the area of drug delivery. Liposomes, polymeric nanoparticles, micelles, dendrimers, lipid nanoparticles, solid lipid nanoparticles, protein-based carriers, and inorganic nanomaterials have been investigated for delivery of small molecules, proteins, peptides, nucleic acids, and other therapeutic agents. These systems can protect cargo from premature degradation and can alter the pharmacokinetic behavior of therapeutic compounds (3).

Targeted drug delivery aims to increase the concentration of a therapeutic agent at the intended site while limiting exposure to non-target tissues. Targeting may be passive, active, or stimulus-responsive. Passive targeting takes advantage of differences in tissue architecture and vascular permeability, whereas active targeting uses ligands that interact with receptors or other molecular structures on target cells. Stimulus-responsive systems are designed to release therapeutic cargo in response to specific physicochemical or biological conditions (4).

Cancer therapy has been one of the most extensively investigated applications of targeted nanomedicine. Nanocarriers can potentially improve accumulation and retention of therapeutic molecules in tumors and can be functionalized with antibodies, peptides, aptamers, or other ligands. However, recent research has also demonstrated that the biological behavior of nanoparticles is more complex than originally assumed. Tumor heterogeneity, variable vascular permeability, cellular uptake, and nanoparticle clearance can substantially affect delivery efficiency (5).

The clinical translation of nanomedicine remains challenging. Although several nanotechnology-based formulations have reached clinical use, many promising systems remain at the preclinical or early clinical stage. A major translational issue is the difference between nanoparticle behavior in experimental models and in humans. Manufacturing, reproducibility, regulatory requirements, toxicity assessment, and long-term biological effects also require careful consideration (6, 7).

Recent research has consequently shifted from simply developing new nanoparticles toward understanding their complete biological journey. This includes circulation, protein corona formation, tissue penetration, cellular uptake, intracellular trafficking, drug release, metabolism, and clearance. A better understanding of these processes is necessary for developing predictable and clinically useful targeted drug-delivery systems (5).

2. Nanocarriers used in targeted drug delivery

2.1 Liposomes

Liposomes are spherical vesicles composed mainly of phospholipid bilayers surrounding an aqueous core. They can encapsulate hydrophilic molecules within the aqueous compartment and hydrophobic molecules within the lipid bilayer. Their composition and surface properties can be modified to influence circulation time, stability, and tissue distribution. Liposomes have been extensively investigated for anticancer, antimicrobial, vaccine, and other therapeutic applications. Surface modification using polyethylene glycol or targeting ligands can alter their biological behavior. Their ability to encapsulate diverse pharmaceutical compounds makes them one of the most established nanocarrier platforms.

2.2 Lipid nanoparticles

Lipid nanoparticles have become particularly important for delivery of nucleic acids, including messenger RNA and small interfering RNA. Their development has demonstrated that nanoscale lipid systems can protect fragile nucleic acids and facilitate cellular delivery.

Recent research has focused on improving the *in vivo* behavior of lipid nanoparticles through optimization of lipid composition, particle size, surface properties, cargo loading, and manufacturing conditions. Quality-by-design approaches are increasingly being investigated to improve reproducibility and translation of RNA-delivery systems (8).

2.3 Polymeric nanoparticles

Polymeric nanoparticles are prepared from biodegradable or biocompatible polymers and can provide controlled release of therapeutic molecules. Polymers such as PLGA have been extensively investigated because their degradation properties can be modified through formulation parameters.

Polymeric nanoparticles may be engineered to respond to biological conditions or to display targeting ligands. Their potential applications include cancer therapy, antimicrobial delivery, gene delivery, and controlled release of conventional pharmaceuticals.

2.4 Polymeric micelles

Polymeric micelles are self-assembled structures formed from amphiphilic polymers. Their hydrophobic core can accommodate poorly water-soluble compounds, while their hydrophilic outer region interacts with the aqueous biological environment.

Their ability to improve the apparent solubility of hydrophobic drugs makes them attractive for pharmaceutical formulations. However, micelle stability after administration and premature drug release remain important considerations.

2.5 Dendrimers

Dendrimers are highly branched, nanoscale macromolecules with relatively well-defined structures. Their internal cavities and surface functional groups provide opportunities for drug encapsulation or chemical conjugation. Surface modification can alter dendrimer toxicity, solubility, cellular uptake, and targeting behavior. Their multifunctional surface makes them particularly interesting for systems combining drug delivery and molecular targeting.

2.6 Solid lipid nanoparticles and nanostructured lipid carriers

Solid lipid nanoparticles use solid lipids as the main structural component, while nanostructured lipid carriers generally combine solid and liquid lipids. These systems can improve drug stability and provide controlled release. Their relatively favorable biocompatibility and ability to incorporate lipophilic compounds have stimulated research in oral, topical, ocular, and systemic drug delivery.

2.7 Inorganic and hybrid nanoparticles

Gold nanoparticles, silica nanoparticles, iron oxide nanoparticles, and other inorganic systems have been investigated for drug delivery, imaging, photothermal therapy, and theranostics. Hybrid systems combine two or more material classes to provide multiple functions.

However, inorganic nanoparticles require careful toxicity and clearance evaluation. Their persistence, surface chemistry, and interactions with biological tissues can differ substantially from biodegradable organic carriers.

3. Targeting strategies

3.1 Passive targeting

Passive targeting relies on physiological and pathological differences between diseased and healthy tissues. In cancer research, the enhanced permeability and retention (EPR) effect has historically been used as a major conceptual basis for nanoparticle accumulation in tumors. However, recent research has highlighted substantial variability in the EPR effect among tumors and patients. Consequently, EPR should not be considered a universal mechanism guaranteeing effective nanoparticle delivery. Tumor vascularization, extracellular matrix composition, interstitial pressure, immune-cell interactions, and particle characteristics all influence delivery (5).

3.2 Active targeting

Active targeting involves attaching ligands to nanoparticle surfaces that recognize specific receptors or molecular structures on target cells. Antibodies, antibody fragments, peptides, aptamers, carbohydrates, and other ligands can be used for this purpose.

After reaching the target tissue, ligand–receptor interactions may promote cellular uptake. Active targeting is therefore particularly attractive when a disease-associated receptor is sufficiently expressed and accessible.

Nevertheless, ligand attachment does not guarantee successful delivery. Nanoparticles must first reach the relevant tissue, cross biological barriers, interact appropriately with the target cells, and release their cargo. These sequential requirements make active targeting a complex biological process.

3.3 Stimulus-responsive targeting

Stimulus-responsive nanoparticles are designed to release therapeutic cargo in response to specific conditions. Internal stimuli include pH, redox conditions, enzymes, and reactive oxygen species, whereas external stimuli may include light, ultrasound, magnetic fields, or temperature.

Such systems can provide greater control over the timing and location of drug release. In tumors, for example, differences in pH, enzyme activity, and redox state can potentially be exploited for selective release.

3.4 Subcellular targeting

Recent nanomedicine research has increasingly focused on targeting intracellular organelles such as mitochondria, lysosomes, endoplasmic reticulum, and Golgi apparatus. Subcellular targeting may allow therapeutic compounds to act directly at specific intracellular locations (9).

This approach represents a further step beyond tissue and cellular targeting. However, intracellular trafficking and endosomal escape remain major challenges, especially for nucleic-acid therapeutics.

4. Biological barriers to nanoparticle delivery

A nanoparticle administered to the body encounters multiple biological barriers before reaching its intended target. These include blood proteins, immune cells, vascular barriers, extracellular matrix, cellular membranes, endosomal compartments, and clearance organs.

4.1 Protein corona

When nanoparticles enter biological fluids, proteins and other biomolecules rapidly adsorb onto their surfaces, forming a protein corona. This corona can alter particle size, surface charge, cellular recognition, circulation, and biodistribution.

Therefore, the biological identity of a nanoparticle may differ from its original engineered surface. Understanding protein corona formation is essential for predicting *in vivo* behavior.

4.2 Mononuclear phagocyte system

Nanoparticles circulating in the bloodstream may be recognized and removed by cells of the mononuclear phagocyte system, particularly in the liver and spleen. Rapid clearance can reduce the fraction of nanoparticles available to reach the target tissue.

Particle size, surface charge, shape, composition, and surface modification influence this process.

4.3 Blood–brain barrier

The blood–brain barrier presents a particularly difficult obstacle for drug delivery to the central nervous system. Tight junctions between endothelial cells and active transport mechanisms restrict entry of many therapeutic compounds.

Engineered nanoparticles have been investigated for receptor-mediated transport, transcytosis, and other approaches to improve brain delivery. Recent reviews identify nanoparticle engineering as a promising strategy but emphasize that brain accumulation remains suboptimal for many systems (10).

4.4 Tumor microenvironment

The tumor microenvironment is heterogeneous and includes cancer cells, immune cells, extracellular matrix, blood vessels, and variable physicochemical conditions. High interstitial pressure and dense extracellular matrix can restrict nanoparticle penetration.

Therefore, effective tumor targeting requires consideration of tissue penetration in addition to receptor recognition.

5. Nanobiotechnology in cancer therapy

Cancer remains one of the major application areas of targeted nanomedicine. Conventional chemotherapy can damage healthy tissues because many anticancer drugs lack sufficient selectivity.

Nanocarriers can potentially improve therapeutic index by changing drug distribution, providing controlled release, and enabling targeting. Liposomal formulations, polymeric nanoparticles, micelles, and other systems have been studied for delivery of chemotherapeutic agents.

Multifunctional nanoparticles may combine therapeutic and diagnostic functions. Such systems are commonly referred to as theranostic platforms and may enable imaging of disease-associated tissues while simultaneously delivering therapy.

Recent research has also explored subcellular targeting within tumor cells. Nanoparticles designed to target mitochondria, lysosomes, or other organelles may provide additional mechanisms for inducing therapeutic responses (9). However, cancer nanomedicine remains limited by tumor heterogeneity and variability in nanoparticle accumulation. Recent work has therefore emphasized the need to move beyond assumptions that all tumors will respond similarly to a particular nanocarrier.

6. Nanoparticles for gene and RNA delivery

The delivery of nucleic acids represents an important application of nanobiotechnology. DNA, mRNA, siRNA, microRNA, and CRISPR-associated components are susceptible to degradation and generally have difficulty crossing cellular membranes. Lipid nanoparticles and other nanocarriers can protect nucleic acids and facilitate cellular uptake. Recent work has investigated lipid nanoparticles for mRNA, siRNA, and CRISPR-related applications (8).

Important challenges include endosomal escape, tissue-specific delivery, immune responses, stability, manufacturing reproducibility, and controlled intracellular release.

The development of RNA therapeutics has consequently increased the importance of nanoparticle engineering. Optimizing lipid composition, particle size, surface chemistry, cargo loading, and manufacturing conditions can significantly affect delivery performance.

7. Nanotechnology in neurological drug delivery

Neurological diseases present major challenges because of the blood–brain barrier. Many potentially effective drugs cannot reach therapeutic concentrations in the brain after conventional systemic administration.

Engineered nanoparticles have been investigated for improving CNS delivery through receptor-mediated transport, surface modification, and other mechanisms. Nanocarriers may also protect therapeutic molecules from degradation and potentially provide controlled release.

Recent reviews emphasize that CNS nanomedicine must address several sequential barriers, including circulation, brain endothelial interaction, transcytosis, extracellular transport, cellular uptake, and intracellular release (10).

Potential applications include delivery of drugs for Alzheimer's disease, Parkinson's disease, brain tumors, neuroinflammation, and other neurological conditions. However, clinical translation remains challenging and requires stronger evidence regarding long-term safety and brain biodistribution.

8. Antimicrobial and other therapeutic applications

Nanobiotechnology is also being investigated for antimicrobial drug delivery. Nanocarriers may improve the stability, solubility, localization, and controlled release of antimicrobial compounds.

Targeted antimicrobial delivery may be useful where high local concentrations are desirable while systemic exposure is minimized. Nanocarriers have also been explored for delivery of antimicrobial peptides and nucleic-acid-based approaches. Other therapeutic applications include cardiovascular disease, inflammatory disorders, ophthalmic diseases, dermatological conditions, vaccine delivery, and regenerative medicine.

Recent comprehensive reviews describe applications of nano-formulations across oncology, pulmonary, cardiovascular, endocrine, dermatological, and ophthalmic diseases (3).

9. Theranostics and multifunctional nanoplatforms

Theranostics combines diagnosis and therapy in a single platform. Nanoparticles can be engineered to carry therapeutic molecules while also providing imaging signals.

For example, magnetic, optical, or other imaging-active components can potentially be incorporated into nanocarriers. This can provide information about biodistribution and treatment response.

Multifunctional nanoparticles may also combine targeting ligands, therapeutic cargo, imaging components, and stimulus-responsive release mechanisms. Such complexity may increase functionality but also creates additional challenges in manufacturing, characterization, quality control, and regulatory approval.

Therefore, multifunctionality must be balanced against formulation complexity.

10. Recent advances in nanocarrier design

Recent advances have focused on developing nanoparticles that are more predictable, biodegradable, responsive, and biologically compatible. One important development is the use of biodegradable nanocarriers, which are designed to degrade into products that can be eliminated from the body. Biodegradability may help reduce concerns regarding long-term accumulation.

Another development is hybrid nanocarriers, which combine the advantages of different materials. For example, lipid–polymer hybrid nanoparticles can potentially combine the stability of polymeric systems with the biological compatibility of lipid components.

Stimulus-responsive systems represent another major area. By responding to local pH, enzymes, redox conditions, light, temperature, or other signals, these systems may provide more controlled drug release.

Artificial intelligence and computational modeling are also increasingly being considered for nanomedicine design. AI may assist with optimization of nanoparticle composition, prediction of biological interactions, formulation screening, and analysis of complex pharmacokinetic datasets. Recent reviews identify AI-driven nanocarriers as an emerging direction for precision delivery (4).

11. Safety and toxicological considerations

Safety is a fundamental requirement for clinical translation of nanomedicines. Nanoparticles can interact with proteins, cell membranes, immune cells, organs, and biological barriers in ways that differ from conventional pharmaceutical molecules.

Potential concerns include oxidative stress, inflammation, immunogenicity, cytotoxicity, organ accumulation, and unexpected interactions with biological systems. These effects depend strongly on particle composition, size, surface characteristics, dose, route of administration, and duration of exposure.

Therefore, safety evaluation should consider not only the therapeutic molecule but also the nanocarrier and its degradation products.

Long-term toxicity can be difficult to predict from short-term studies. Standardized toxicological protocols and long-term follow-up are important for nanomedicines intended for repeated administration.

12. Manufacturing and regulatory challenges

One of the major barriers to clinical translation is reproducible manufacturing. Nanoparticle properties can be sensitive to relatively small changes in formulation conditions.

Critical quality attributes may include particle size, size distribution, surface charge, morphology, drug loading, encapsulation efficiency, release profile, sterility, and stability.

Large-scale manufacturing must maintain these characteristics consistently. Processes that work effectively at laboratory scale may behave differently during industrial production.

Regulatory evaluation also requires characterization of the nanocarrier, therapeutic payload, manufacturing process, stability, pharmacokinetics, biodistribution, and toxicology.

The DELIVER framework proposed for nanomedicine translation emphasizes understanding physicochemical properties, biological exposure, reproducibility, biocompatibility, scale-up, good manufacturing practice, and regulatory requirements before clinical investigation (11-14).

13. Current challenges

Despite significant progress, several challenges remain:

- Biological variability: Nanoparticle behavior can differ between animal models and humans.
- Targeting efficiency: A nanoparticle reaching a diseased tissue does not necessarily mean that it will enter the appropriate cells or release its cargo effectively.
- Tumor heterogeneity: Cancer tissues may vary considerably in vascularity, receptor expression, extracellular matrix, and immune environment.
- Protein corona: Adsorbed biomolecules can change the effective biological identity of nanoparticles.
- Toxicity: Some nanomaterials may cause undesirable cellular or immune responses.
- Scale-up: Laboratory-scale synthesis may not translate directly to industrial manufacturing.
- Regulation: Complex nanomedicines require extensive characterization and quality control.

- Cost: Advanced multifunctional formulations may be expensive to manufacture and characterize.

These challenges indicate that the future of nanomedicine depends not only on developing novel materials but also on understanding biological mechanisms and improving translational predictability.

14. Future perspectives

Future research is likely to focus on more predictable and personalized nanomedicine. Patient-specific characteristics, including disease phenotype, receptor expression, immune status, and biological barriers, may eventually be incorporated into nanocarrier design.

AI and machine learning may assist in predicting nanoparticle behavior and optimizing formulation parameters. Multi-omics technologies may provide information about disease-specific molecular environments that can be exploited for targeted delivery.

Another promising direction is the development of biomimetic nanoparticles, which use biological membranes or biomolecular components to improve biological compatibility and targeting.

Precision nanomedicine may ultimately involve selecting or designing a nanocarrier according to the characteristics of an individual patient rather than applying the same formulation to all patients.

However, successful translation will require collaboration among biotechnology, pharmaceutical science, nanotechnology, medicine, toxicology, manufacturing, and regulatory disciplines.

15. Conclusion

Nanobiotechnology has substantially expanded the possibilities of targeted drug delivery by providing nanoscale systems capable of improving drug solubility, stability, pharmacokinetics, controlled release, and tissue-specific delivery. Liposomes, lipid nanoparticles, polymeric nanoparticles, micelles, dendrimers, solid lipid nanoparticles, and hybrid systems represent important platforms for delivering conventional drugs as well as proteins and nucleic acids.

Targeting can be achieved through passive mechanisms, ligand-mediated active targeting, stimulus-responsive release, and increasingly sophisticated subcellular targeting. These approaches have potential applications in cancer, neurological disorders, infectious diseases, genetic disorders, and other therapeutic areas.

Nevertheless, successful nanoparticle design does not automatically translate into clinical efficacy. Biological barriers, protein corona formation, heterogeneous disease environments, immune interactions, toxicity, manufacturing variability, scale-up, and regulatory requirements remain significant challenges. Recent translational research emphasizes that better understanding of nanoparticle biodistribution, tissue accessibility, pharmacokinetics, and clearance is essential for clinical success.

The future of nanobiotechnology is likely to involve biodegradable and multifunctional nanocarriers, AI-assisted formulation design, biomimetic systems, stimulus-responsive delivery, RNA therapeutics, and personalized nanomedicine. Continued integration of biotechnology, nanotechnology, pharmacology, and clinical research may allow targeted drug delivery systems to become more predictable, safer, and therapeutically effective.

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