



WISELEAF SCIENTIFIC VENTURES

NANOPARTICLE MEDIATED DRUG DELIVERY SYSTEMS FOR CANCER TREATMENT

Chapter 5: Surface Functionalization and Targeting Approaches of Nanoparticles

**Mr. Vitthal B. Kundgir¹, Ms. Sharwari K. Sonawane², Dr. Shivraj P.
Jadhav³**

^{1,2}Research Scholar, Divine College of Pharmacy, Satana, Nashik, Maharashtra.

³Assistant Professor, Department of Pharmaceutics, Divine College of Pharmacy, Satana

Abstract:

Nanoparticle-based drug delivery systems have emerged as a promising platform for improving the therapeutic efficacy and safety of conventional pharmaceuticals. The biological performance of these systems is largely governed by their surface characteristics, which influence stability, biodistribution, cellular uptake, and interactions with physiological environments. Surface functionalization has therefore become an essential strategy for enhancing the pharmacokinetic and pharmacodynamic properties of nanocarriers. Techniques such as polymer coating, PEGylation, ligand conjugation, and biomimetic modifications have been extensively explored to improve biocompatibility, prolong systemic circulation, and facilitate selective accumulation at target sites. Targeting approaches employed in nanomedicine include passive, active, and stimuli-responsive mechanisms. Passive targeting utilizes the pathological characteristics of diseased tissues, whereas active targeting relies on the attachment of specific ligands capable of recognizing cellular receptors. Stimuli-responsive systems provide additional control over drug release by responding to internal or external triggers, thereby increasing therapeutic precision and reducing off-target effects.

Surface-functionalized nanoparticles have demonstrated considerable potential in the treatment of cancer, neurological disorders, infectious diseases, cardiovascular conditions, and in gene delivery applications. Nevertheless, challenges associated with protein corona formation, biological barriers, large-scale manufacturing, regulatory requirements, and clinical translation continue to influence their successful development. This chapter presents an overview of the fundamental principles, surface engineering strategies, targeting approaches, therapeutic





WISELEAF SCIENTIFIC VENTURES

applications, and future perspectives of functionalized nanoparticles, highlighting their growing importance in the advancement of precision nanomedicine.

Keywords: Nanoparticles; Surface Functionalization; Targeted Drug Delivery; Active Targeting; PEGylation; Nanomedicine

1. Introduction

Nanotechnology has significantly transformed the field of drug delivery by providing innovative approaches to improve the therapeutic performance of pharmaceutical agents. Nanoparticle-based drug delivery systems offer several advantages over conventional dosage forms, including enhanced solubility of poorly water-soluble drugs, controlled and sustained drug release, improved bioavailability, and selective delivery to target tissues. These properties have expanded the application of nanocarriers in the treatment of cancer, infectious diseases, neurological disorders, cardiovascular diseases, and other chronic conditions (1). The clinical effectiveness of nanoparticles is not solely dependent on their core composition but is largely influenced by their surface characteristics. When nanoparticles enter biological systems, they interact with proteins, cells, and physiological barriers that determine their circulation time, bio distribution, cellular uptake, and therapeutic efficacy. Consequently, surface functionalization has emerged as a key strategy for optimizing nanoparticle behavior and enhancing their biomedical performance (2).

Surface engineering involves the modification of nanoparticle surfaces through the incorporation of polymers, ligands, antibodies, peptides, aptamers, and biomimetic materials. These modifications can improve colloidal stability, reduce immune recognition, prolong systemic circulation, and facilitate site-specific drug delivery (3). In addition, the integration of targeting molecules onto nanoparticle surfaces enables selective interaction with diseased cells, thereby increasing therapeutic efficiency while minimizing off-target effects. Recent advances in nanomedicine have also led to the development of multifunctional and stimuli-responsive nanoparticles that can release therapeutic agents in response to specific biological or external triggers. Such innovations have created new opportunities for precision medicine and personalized therapy. However, several challenges, including biological barriers, protein corona formation, large-scale manufacturing, and clinical translation, continue to influence the successful application of these systems (4).

1.1 Evolution of Nanoparticle Drug Delivery

The development of nanoparticle-based drug delivery originated from the need to overcome the limitations associated with conventional pharmaceutical formulations, such as poor drug solubility, rapid metabolism, nonspecific distribution, and systemic toxicity (5). Early nanocarrier systems were primarily designed to improve drug stability and prolong circulation time. Over time, advancements in materials science and nanotechnology led to the development of diverse platforms, including liposomes, polymeric nanoparticles, Dendrimers, solid lipid nanoparticles, nanostructured lipid carriers, metallic nanoparticles, and hybrid nanocarriers. A





WISELEAF SCIENTIFIC VENTURES

major advancement in this field was the introduction of targeted drug delivery concepts, where nanoparticles were engineered to accumulate preferentially at disease sites. More recently, the focus has shifted toward multifunctional nanocarriers capable of combining drug delivery, imaging, and diagnostic functions within a single platform. These developments have established nanotechnology as an important component of modern therapeutic strategies (6).

1.2 Importance of Surface Functionalization

Surface functionalization is a critical determinant of nanoparticle performance because the surface represents the first point of contact with the biological environment. Appropriate surface modification can significantly influence nanoparticle stability, bio distribution, pharmacokinetics, and cellular interactions. Functionalization strategies such as PEGylation, polymer coating, ligand conjugation, and biomimetic surface engineering are widely used to reduce nonspecific protein adsorption and immune clearance while enhancing target specificity (7). Surface-bound ligands enable receptor-mediated uptake by specific cells or tissues, thereby improving therapeutic efficacy and reducing adverse effects. In addition, smart surface modifications that respond to pH, temperature, enzymes, or redox conditions provide controlled and site-specific drug release. The ability to tailor surface properties has transformed nanoparticles into highly sophisticated drug delivery platforms suitable for a wide range of biomedical applications.

1.3 Scope of the Chapter

This chapter presents an overview of the fundamental concepts and recent developments in nanoparticle surface functionalization and targeting approaches. It discusses the major strategies used for surface modification, the mechanisms of passive and active targeting, and the role of different ligands in enhancing drug delivery efficiency. The chapter also highlights important therapeutic applications, current challenges, and future perspectives of surface-engineered nanoparticles in the advancement of precision nanomedicine.

2. Fundamentals of Surface Functionalization

Surface functionalization is a fundamental strategy in nanomedicine that involves modifying the outer surface of nanoparticles to improve their physicochemical characteristics, biological interactions, and therapeutic performance. Since the nanoparticle surface is the primary interface with the biological environment, its properties largely determine circulation behavior, biodistribution, cellular uptake, and overall treatment efficacy. Appropriate surface modification can enhance stability, reduce immune recognition, improve target specificity, and facilitate controlled drug delivery. Therefore, understanding the fundamental principles governing nanoparticle surface properties is essential for the rational design of advanced nanocarriers systems.

2.1 Concept and Objectives

Surface functionalization refers to the intentional modification of nanoparticle surfaces through the attachment of specific molecules, polymers, ligands, or biological components to impart





WISELEAF SCIENTIFIC VENTURES

desired functions. The primary objectives of surface functionalization include improving colloidal stability, minimizing aggregation, prolonging circulation time, enhancing biocompatibility, and enabling site-specific delivery of therapeutic agents (8). In addition, functionalized surfaces can facilitate receptor-mediated cellular uptake and controlled drug release. By tailoring surface characteristics, nanoparticles can be engineered to overcome physiological barriers and achieve improved therapeutic outcomes. Consequently, surface engineering has become a critical component in the development of modern drug delivery systems (9).

2.2 Surface Properties Influencing Biological Performance

The biological behavior of nanoparticles is strongly influenced by their surface properties. Characteristics such as particle size, shape, surface charge, and hydrophobicity affect interactions with biological fluids, cells, and tissues, ultimately determining therapeutic efficacy.

2.2.1 Particle Size and Shape

Particle size plays a crucial role in nanoparticle bio distribution, cellular uptake, and clearance. Nanoparticles within the size range of approximately 10-200 nm are generally considered suitable for drug delivery applications because they can avoid rapid renal elimination while maintaining efficient tissue penetration (10). Smaller particles often demonstrate enhanced cellular internalization, whereas larger particles may exhibit prolonged retention at target sites. Particle shape also affects biological performance. Although spherical nanoparticles are the most commonly used, rod-shaped, tubular, and disc-shaped particles may exhibit different circulation profiles and cellular uptake mechanisms. Optimization of particle size and shape is therefore important for achieving efficient drug delivery and therapeutic effectiveness.

2.2.2 Surface Charge

Surface charge influences nanoparticle stability and interactions with cellular membranes (11). It is commonly assessed through zeta potential measurements, which provide information regarding colloidal stability and electrostatic behavior. Positively charged nanoparticles generally exhibit enhanced cellular uptake because of electrostatic attraction to negatively charged cell membranes. However, highly cationic surfaces may also increase cytotoxicity and trigger immune responses. Neutral or slightly negative nanoparticles often demonstrate improved biocompatibility and prolonged circulation, making them attractive for systemic drug delivery applications (12).

2.2.3 Hydrophobicity and Hydrophilicity

The balance between hydrophobicity and Hydrophilicity significantly affects nanoparticle interactions with biological systems. Hydrophobic surfaces tend to adsorb plasma proteins more readily, which may accelerate immune clearance and alter bio distribution. In contrast, hydrophilic surfaces improve aqueous stability and reduce nonspecific protein adsorption. Hydrophilic polymer coatings such as polyethylene glycol (PEG) are frequently employed to





WISELEAF SCIENTIFIC VENTURES

create a protective hydration layer around nanoparticles, thereby enhancing circulation time and minimizing recognition by the immune system. Appropriate control of surface hydrophobicity is therefore essential for optimizing nanoparticle performance (13).

2.3 Protein Corona Formation and Nano-Bio Interface

When nanoparticles are introduced into biological fluids, their surfaces rapidly interact with proteins, lipids, and other biomolecules. This interaction leads to the formation of a biomolecular layer known as the protein corona. The protein corona effectively alters the biological identity of nanoparticles and influences their interactions with cells and tissues. The composition of the protein corona depends on nanoparticle size, surface charge, hydrophobicity, and chemical composition, as well as the characteristics of the surrounding biological environment. Protein adsorption can affect biodistribution, cellular uptake, immune recognition, and therapeutic efficacy. In some cases, the protein corona may mask targeting ligands and reduce targeting efficiency. The nano-bio interface represents the dynamic region where engineered nanoparticles interact with biological systems. Understanding these interactions is essential for predicting nanoparticle behavior in vivo and designing surface modifications that maintain functionality under physiological conditions (14).

2.4 Biological Barriers in Nanoparticle Delivery

The successful delivery of nanoparticles to target tissues requires overcoming multiple biological barriers. Following administration, nanoparticles encounter immune surveillance mechanisms that can promote rapid clearance from circulation. Macrophages of the mononuclear phagocyte system, particularly those located in the liver and spleen, play a major role in removing foreign particles. Vascular barriers also influence nanoparticle transport from the bloodstream to target tissues. After extravasation, nanoparticles must diffuse through the extracellular matrix before reaching target cells (15). Cellular membranes subsequently represent another barrier, requiring efficient internalization mechanisms for therapeutic action. Certain organs possess highly specialized barriers, such as the blood-brain barrier, which restricts the entry of many therapeutic agents into the central nervous system. Surface functionalization strategies are therefore frequently employed to enhance barrier penetration, improve targeting efficiency, and maximize therapeutic outcomes. A comprehensive understanding of these biological barriers is critical for the successful design and clinical translation of nanoparticle-based drug delivery systems (16).

3. Surface Functionalization Strategies

Surface functionalization strategies are employed to modify nanoparticle surfaces in order to improve stability, biocompatibility, circulation time, targeting efficiency, and therapeutic performance. Depending on the nature of the interaction between the modifying agent and the nanoparticle surface, these strategies can be broadly classified into physical, chemical, polymer-based, and biomimetic approaches. Each method offers unique advantages and is selected based on the intended biomedical application.





WISELEAF SCIENTIFIC VENTURES

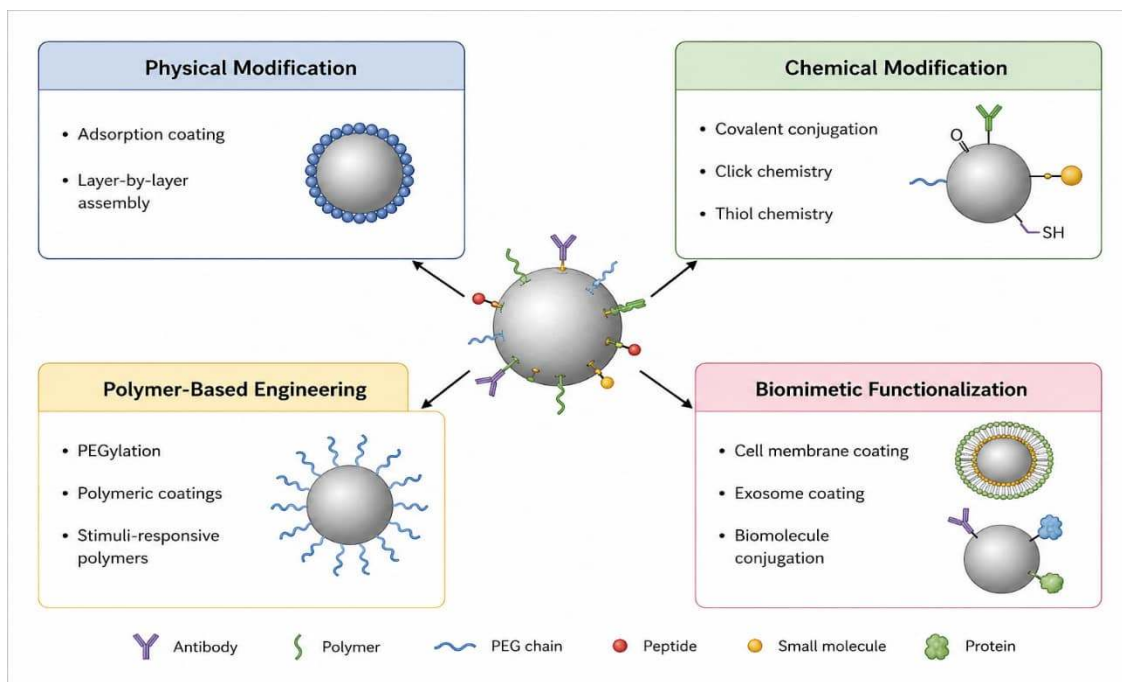


Fig.1 Major Surface Functionalization Strategies for Nanoparticle Engineering (17)

3.1 Physical Modification Techniques

Physical modification involves the attachment of functional materials onto nanoparticle surfaces through non-covalent interactions such as electrostatic attraction, hydrogen bonding, hydrophobic interactions, and van der Waals forces. These methods are generally simple, cost-effective, and suitable for preserving the biological activity of sensitive molecules.

3.1.1 Adsorption Coating

Adsorption coating is one of the simplest methods of surface functionalization, in which polymers, proteins, surfactants, or other biomolecules are physically adsorbed onto nanoparticle surfaces. The process is driven by intermolecular interactions and can improve colloidal stability, biocompatibility, and cellular interactions. Although adsorption-based coatings are easy to prepare, their stability may be affected by changes in physiological conditions and competitive displacement by plasma proteins.

3.1.2 Layer-by-Layer Assembly

Layer-by-layer (LbL) assembly involves the sequential deposition of oppositely charged materials onto nanoparticle surfaces, resulting in the formation of multilayer coatings. This technique provides precise control over coating thickness and composition while enabling the incorporation of therapeutic agents, targeting ligands, and responsive materials. LbL-modified nanoparticles have shown potential in controlled drug delivery and multifunctional nanocarrier design (18).





WISELEAF SCIENTIFIC VENTURES

3.2 Chemical Modification Techniques

Chemical surface modification relies on the formation of stable covalent bonds between nanoparticle surfaces and functional molecules. Compared with physical approaches, chemical techniques generally provide greater stability and long-term functionality under physiological conditions.

3.2.1 Covalent Conjugation

Covalent conjugation involves the attachment of therapeutic agents, polymers, peptides, antibodies, or targeting ligands through stable chemical linkages. Functional groups such as amino, carboxyl, hydroxyl, and thiol groups are commonly utilized for conjugation reactions. This strategy improves ligand retention and enhances targeting efficiency by minimizing premature detachment of surface-bound molecules.

3.2.2 Click Chemistry

Click chemistry refers to a group of highly selective and efficient chemical reactions used for nanoparticle functionalization. These reactions occur under mild conditions and generate minimal by-products, making them suitable for biomedical applications. Click chemistry enables precise attachment of targeting ligands, imaging probes, and biomolecules while preserving their biological activity.

3.2.3 Thiol Chemistry

Thiol chemistry is widely employed for the functionalization of metallic nanoparticles, particularly gold nanoparticles. Thiol-containing molecules form strong metal–sulfur bonds, producing highly stable surface modifications. This approach allows controlled immobilization of proteins, peptides, nucleic acids, and other bioactive molecules, making it valuable for targeted drug delivery and diagnostic applications (19).

3.3 Polymer-Based Surface Engineering

Polymer-based surface engineering is among the most extensively used approaches in nanomedicine. Polymer coatings improve nanoparticle stability, reduce immune recognition, and facilitate controlled drug release.

3.3.1 PEGylation

PEGylation involves the attachment of polyethylene glycol (PEG) chains to nanoparticle surfaces. The hydrophilic PEG layer reduces protein adsorption and recognition by the mononuclear phagocyte system, thereby prolonging circulation time and enhancing systemic stability. PEGylation has become a widely adopted strategy in clinically approved nanomedicine formulations.

3.3.2 Polymeric Coatings

Natural and synthetic polymers such as chitosan, dextran, alginate, and poly(lactic-co-glycolic acid) are frequently used as surface coatings. These polymers enhance colloidal stability, protect encapsulated drugs from degradation, and provide functional groups for further ligand





WISELEAF SCIENTIFIC VENTURES

attachment. Polymeric coatings also contribute to improved biocompatibility and controlled drug release.

3.3.3 Stimuli-Responsive Polymers

Stimuli-responsive polymers are designed to undergo structural or physicochemical changes in response to specific environmental triggers such as pH, temperature, enzymes, or redox conditions. These smart materials enable site-specific drug release and improve therapeutic precision by responding selectively to disease-associated microenvironments (20).

3.4 Biomimetic Functionalization

Biomimetic functionalization aims to mimic natural biological systems to improve nanoparticle compatibility, targeting capability, and circulation behavior. These approaches have emerged as promising alternatives to conventional synthetic surface modifications (21).

3.4.1 Cell Membrane-Coated Nanoparticles

Cell membrane-coated nanoparticles are produced by covering synthetic nanoparticle cores with membranes derived from natural cells such as erythrocytes, platelets, leukocytes, or cancer cells. The membrane coating preserves native surface proteins and biological functions, enabling immune evasion, prolonged circulation, and enhanced tissue-specific targeting.

3.4.2 Exosome-Inspired Systems

Exosome-inspired nanocarriers mimic naturally occurring extracellular vesicles involved in intercellular communication. These systems exhibit excellent biocompatibility and intrinsic targeting capabilities while serving as efficient carriers for drugs, proteins, and nucleic acids. Their natural origin makes them attractive candidates for advanced therapeutic applications.

3.4.3 Bio hybrid Nanoparticles

Biohybrid nanoparticles integrate synthetic nanomaterials with biological components to combine the advantages of both systems. These hybrid platforms offer enhanced stability, improved targeting efficiency, and reduced immunogenicity. Owing to their multifunctional nature, biohybrid systems are increasingly being explored for applications in targeted therapy, diagnostics, and personalized medicine. The selection of an appropriate surface functionalization strategy depends on the desired therapeutic objective, physicochemical characteristics of the nanocarrier, and biological environment. Advances in surface engineering continue to drive the development of next-generation nanoparticles with improved efficacy, safety, and clinical applicability (22).

4. Targeting Approaches in Nanoparticle Drug Delivery

Targeted drug delivery is one of the most important advantages of nanoparticle-based therapeutic systems. Conventional drug administration often results in nonspecific distribution of drugs throughout the body, leading to reduced therapeutic efficacy and increased adverse effects. Nanoparticles can be engineered to selectively accumulate at disease sites, thereby improving drug concentration at the target tissue while minimizing exposure to healthy organs.





WISELEAF SCIENTIFIC VENTURES

Depending on the mechanism employed, nanoparticle targeting strategies are generally classified into passive targeting, active targeting, and stimuli-responsive targeting.

4.1 Passive Targeting

Passive targeting relies on the natural physiological and pathological characteristics of diseased tissues to achieve nanoparticle accumulation. The most widely recognized mechanism is the enhanced permeability and retention (EPR) effect, which is commonly observed in solid tumors and inflamed tissues. Due to rapid and abnormal angiogenesis, tumor blood vessels often possess large endothelial gaps that allow nanoparticles to extravasate and accumulate within the tumor microenvironment. In addition, impaired lymphatic drainage in tumors promotes prolonged retention of nanoparticles at the disease site.

The efficiency of passive targeting is influenced by factors such as nanoparticle size, surface charge, circulation time, and vascular permeability. Nanoparticles with prolonged systemic circulation are more likely to reach and accumulate within target tissues. Although passive targeting has contributed significantly to the success of several nanomedicine formulations, its effectiveness may vary among patients and disease conditions due to biological heterogeneity.

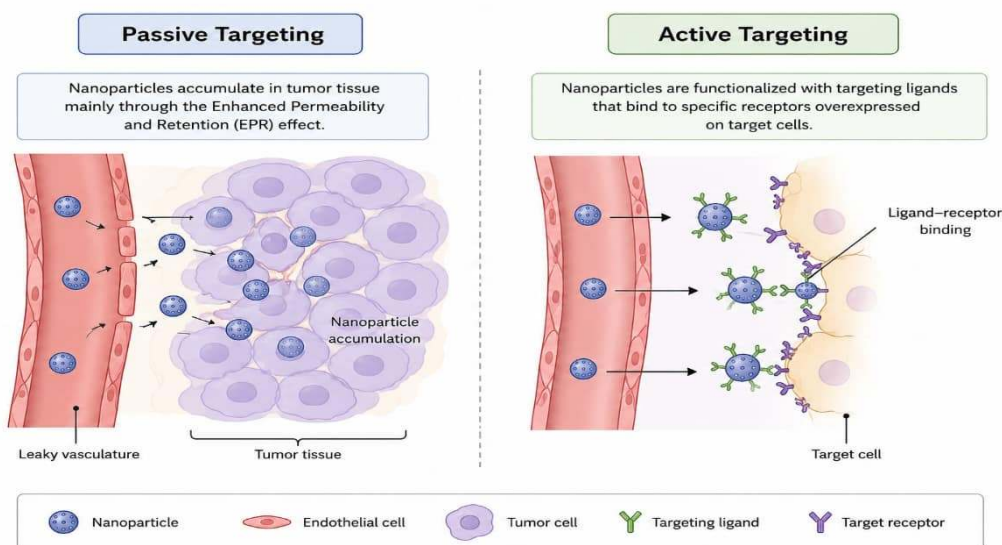


Fig.2 Schematic representation of passive and active targeting mechanisms in nanoparticle-based drug delivery (23) .

4.2 Active Targeting

Active targeting involves the modification of nanoparticle surfaces with specific ligands capable of recognizing and binding to receptors or biomarkers that are overexpressed on target cells. These ligands may include antibodies, peptides, aptamers, carbohydrates, or small molecules. Following ligand-receptor interaction, nanoparticles can undergo receptor-mediated endocytosis, leading to enhanced intracellular delivery of therapeutic agents. Active





WISELEAF SCIENTIFIC VENTURES

targeting improves treatment specificity and reduces off-target effects by directing nanoparticles toward diseased cells while minimizing interactions with healthy tissues. This approach has been extensively investigated in cancer therapy, where nanoparticles are functionalized to target receptors such as folate receptors, transferrin receptors, epidermal growth factor receptors, and integrins. Active targeting can also be applied in neurological disorders, cardiovascular diseases, and infectious diseases to improve therapeutic outcomes.

4.3 Stimuli-Responsive Targeting

Stimuli-responsive targeting represents an advanced strategy in which nanoparticles are engineered to respond to specific internal or external stimuli. These smart nanocarriers remain relatively stable during circulation but undergo structural or functional changes upon exposure to particular triggers, resulting in controlled drug release at the desired site. Internal stimuli include pH variations, enzyme activity, redox potential, and hypoxic conditions commonly associated with pathological tissues. For example, pH-responsive nanoparticles can release drugs preferentially within the acidic microenvironment of tumors or intracellular compartments. External stimuli such as temperature, light, ultrasound, and magnetic fields can also be used to regulate drug release and enhance targeting precision.

Stimuli-responsive nanoparticles offer several advantages, including improved therapeutic control, reduced systemic toxicity, and enhanced treatment efficacy. Ongoing advances in smart nanomaterials continue to expand the potential of this approach for precision medicine and personalized drug delivery. Collectively, passive, active, and stimuli-responsive targeting strategies have significantly improved the effectiveness of nanoparticle-based drug delivery systems. The integration of these approaches with advanced surface functionalization techniques has enabled the development of highly selective and efficient nanocarriers for a wide range of biomedical applications (24).

5. Ligands Used for Targeted Delivery

The success of active nanoparticle targeting largely depends on the selection of appropriate ligands that can specifically recognize and bind to target cells or tissues. Surface conjugation of targeting ligands enhances the selectivity of nanocarriers, promotes receptor-mediated cellular uptake, and improves therapeutic efficacy while minimizing off-target effects. Various biological and synthetic ligands have been investigated for targeted drug delivery, among which antibodies, peptides, aptamers, and small-molecule ligands are the most extensively studied (25).

5.1 Antibodies

Antibodies are highly specific biomolecules capable of recognizing and binding to unique antigens expressed on target cells. Antibody-functionalized nanoparticles can selectively deliver therapeutic agents to diseased tissues through antigen–antibody interactions. This strategy has been widely explored in cancer therapy, where nanoparticles are designed to target overexpressed receptors on tumor cells. Despite their high specificity, the clinical application





WISELEAF SCIENTIFIC VENTURES

of antibodies may be limited by their large molecular size, high production cost, and potential immunogenicity.

5.2 Peptides

Peptides are short chains of amino acids that serve as attractive targeting ligands because of their small size, good tissue penetration, ease of synthesis, and relatively low immunogenicity. Peptide-functionalized nanoparticles can selectively bind to specific cellular receptors and facilitate receptor-mediated internalization. They have been extensively investigated for targeted delivery in oncology, cardiovascular diseases, and neurological disorders.

5.3 Aptamers

Aptamers are short single-stranded DNA or RNA molecules that fold into unique three-dimensional structures capable of binding specific molecular targets with high affinity and selectivity. Aptamer-conjugated nanoparticles combine the advantages of molecular recognition with improved stability and ease of chemical modification. Compared with antibodies, aptamers are less immunogenic and can be synthesized with high reproducibility, making them promising ligands for targeted drug and gene delivery.

5.4 Folate and Other Small-Molecule Ligands

Small-molecule ligands are widely used because of their simple structure, low cost, and efficient receptor binding. Among these, folic acid is one of the most extensively investigated targeting molecules due to the overexpression of folate receptors in many cancer cells. Folate-functionalized nanoparticles can enhance selective drug accumulation through receptor-mediated uptake. Other small-molecule ligands, including transferrin, biotin, carbohydrates, and various vitamins, have also been employed to improve targeting efficiency in different disease conditions. These ligands provide an effective means of enhancing nanoparticle selectivity while maintaining favorable pharmacokinetic properties. The selection of an appropriate targeting ligand depends on the nature of the disease, receptor expression profile, nanoparticle characteristics, and intended therapeutic application. Continuous advances in ligand engineering are expected to further improve the precision and clinical potential of targeted nanoparticle drug delivery systems.

Table 1 Major Targeting Ligands and Their Receptors in Nanomedicine (26)

Ligand Type	Target	Major Advantages	Representative Applications
Antibodies	Cell-surface antigens	High specificity	Cancer therapy
Peptides	Cellular receptors	Small size, good penetration	Tumor and vascular targeting





WISELEAF SCIENTIFIC VENTURES

Aptamers	Proteins and receptors	Low immunogenicity, easy synthesis	Drug and gene delivery
Folate & Small Molecules	Folate and other receptors	Cost-effective, efficient uptake	Cancer and targeted therapeutics

6. Therapeutic Applications

Surface-functionalized nanoparticles have significantly expanded the scope of targeted drug delivery by improving therapeutic efficacy, reducing systemic toxicity, and enabling site-specific treatment. The integration of advanced surface engineering and targeting strategies has facilitated their application in several biomedical fields, particularly in cancer therapy, neurological disorders, gene delivery, and vaccine development. In addition, emerging applications continue to broaden the clinical potential of nanomedicine.

6.1 Cancer Therapy

Cancer remains the most extensively explored area for nanoparticle-based targeted drug delivery. Surface-functionalized nanoparticles can selectively accumulate in tumor tissues through passive and active targeting mechanisms, thereby increasing the local concentration of anticancer agents while minimizing damage to healthy cells. Functionalization with antibodies, peptides, aptamers, and folate molecules enhances receptor-mediated uptake by cancer cells and improves therapeutic outcomes. Moreover, multifunctional nanoparticles have been developed for combined drug delivery, imaging, and photothermal or photodynamic therapy, offering new opportunities for precision oncology.

6.2 Neurological Disorders

The treatment of neurological diseases is often limited by the presence of the blood–brain barrier, which restricts the entry of many therapeutic agents into the central nervous system. Surface modification of nanoparticles with specific targeting ligands can facilitate transport across this barrier and improve drug delivery to the brain. Functionalized nanoparticles have shown promising potential in the management of disorders such as Alzheimer's disease, Parkinson's disease, brain tumors, and stroke. These systems may enhance drug bioavailability, prolong therapeutic action, and reduce systemic adverse effects.

6.3 Gene Delivery and Vaccines

Nanoparticles have emerged as efficient carriers for nucleic acid therapeutics, including DNA, messenger RNA (mRNA), small interfering RNA (siRNA), and gene-editing components. Surface engineering improves the stability of genetic materials and promotes their cellular uptake while protecting them from enzymatic degradation. In vaccine development, functionalized nanoparticles serve as delivery platforms for antigens and adjuvants, enhancing immune responses and improving vaccine efficacy. Recent advances in nanotechnology-based





WISELEAF SCIENTIFIC VENTURES

vaccines have demonstrated the importance of nanoparticle systems in the prevention and treatment of infectious diseases.

6.4 Other Emerging Applications

Beyond conventional drug delivery, surface-functionalized nanoparticles are being investigated for a variety of emerging biomedical applications. These include targeted antimicrobial therapy, cardiovascular drug delivery, regenerative medicine, immunotherapy, and theranostic systems that combine diagnosis and treatment within a single platform. The incorporation of smart and stimuli-responsive materials has further expanded the capabilities of these nanocarriers, enabling controlled drug release and personalized therapeutic interventions. Ongoing advances in nanotechnology are expected to accelerate the clinical translation of these innovative systems and contribute to the development of next-generation precision medicine.

Table 2 Therapeutic Applications of Functionalized Nanoparticles (27-28)

Application Area	Role of Surface Functionalization	Therapeutic Benefit
Cancer Therapy	Ligand-mediated targeting	Improved tumor selectivity
Neurological Disorders	Blood–brain barrier targeting	Enhanced brain delivery
Gene Delivery and Vaccines	Protection and cellular uptake of nucleic acids	Improved transfection and immune response
Emerging Applications	Smart and multifunctional nanocarriers	Precision and personalized therapy

7. Challenges and Future Perspectives

Despite significant progress in nanoparticle-based drug delivery, several scientific, technical, and regulatory challenges continue to limit the widespread clinical application of surface-functionalized nanocarriers. Variations in biological responses, manufacturing complexities, and safety concerns necessitate the development of more reliable and clinically translatable nanoparticle systems. At the same time, advances in materials science, biotechnology, and computational approaches are creating new opportunities for the evolution of precision nanomedicine.





WISELEAF SCIENTIFIC VENTURES

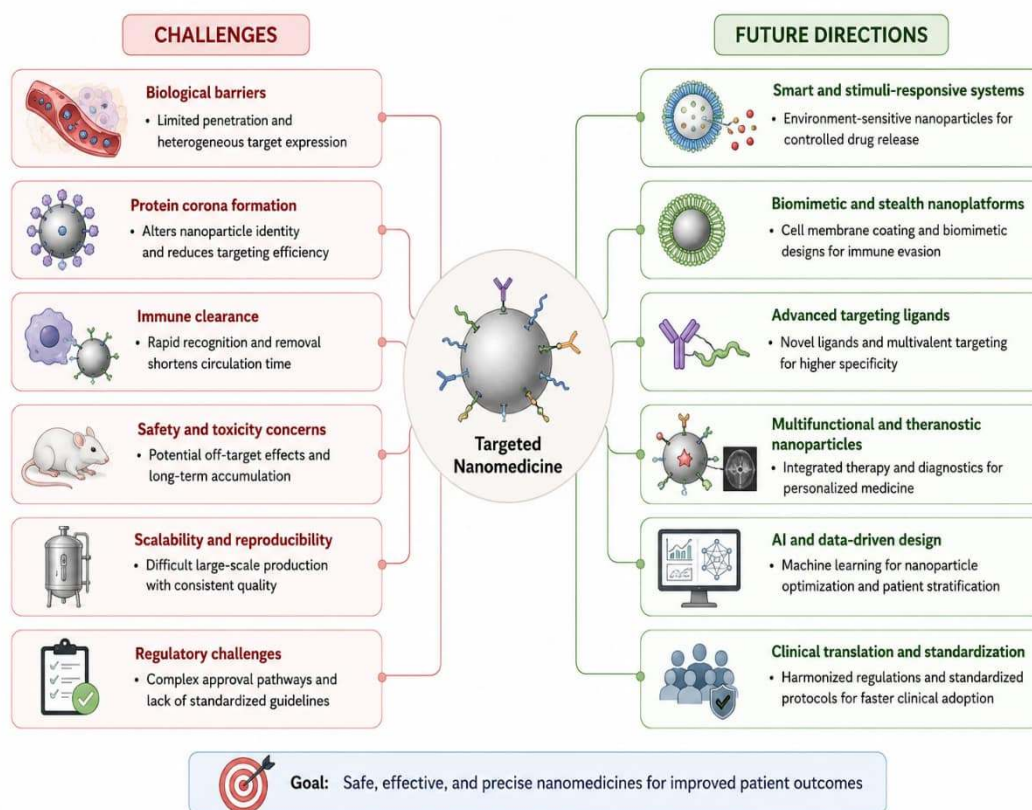


Fig. 3 Schematic representation of the major challenges and future directions in targeted nanomedicine (29).

7.1 Biological and Technical Challenges

The biological performance of nanoparticles is influenced by complex interactions with physiological environments. One of the major challenges is the formation of the protein corona, which can alter the surface properties of nanoparticles and reduce targeting efficiency. In addition, rapid clearance by the mononuclear phagocyte system, limited penetration into target tissues, and biological variability among patients may affect therapeutic outcomes. Technical challenges include reproducible large-scale manufacturing, maintaining physicochemical stability during storage, batch-to-batch consistency, and optimization of surface functionalization processes. The complexity associated with multifunctional nanocarriers may also increase production costs and quality control requirements (30).

7.2 Clinical Translation

Although numerous surface-functionalized nanoparticle systems have demonstrated promising results in preclinical studies, only a limited number have successfully reached clinical application. Translational barriers include long-term safety evaluation, regulatory approval processes, large-scale production, and comprehensive characterization of nanoparticle





WISELEAF SCIENTIFIC VENTURES

behavior in vivo. The establishment of standardized manufacturing protocols and internationally accepted regulatory guidelines is essential for accelerating the clinical development of nanomedicine products. Collaborative efforts among researchers, industry, and regulatory agencies will play an important role in bridging the gap between laboratory research and clinical practice.

7.3 Future Trends in Precision Nanomedicine

Future developments in nanomedicine are expected to focus on the design of highly selective, multifunctional, and personalized drug delivery systems. Smart nanoparticles capable of responding to specific biological stimuli may provide controlled and site-specific drug release with improved therapeutic precision. Biomimetic nanocarriers, biohybrid systems, and advanced surface engineering techniques are likely to enhance biocompatibility and targeting efficiency. Furthermore, the integration of artificial intelligence, machine learning, and computational modeling may facilitate the rational design and optimization of nanoparticle formulations.

The convergence of nanotechnology with molecular diagnostics and personalized medicine is expected to support the development of next-generation therapeutic platforms capable of simultaneous diagnosis, targeted treatment, and real-time monitoring. Continued research and technological innovation will further strengthen the role of surface-functionalized nanoparticles in advancing precision healthcare.

8. Conclusion

Surface functionalization has become a fundamental strategy for enhancing the performance and clinical potential of nanoparticle-based drug delivery systems. By modifying the physicochemical characteristics of nanoparticle surfaces, it is possible to improve stability, prolong systemic circulation, minimize immune recognition, and achieve selective delivery of therapeutic agents to target tissues. Approaches such as physical and chemical modification, polymer-based engineering, and biomimetic functionalization have significantly advanced the development of efficient and multifunctional nanocarriers. The incorporation of passive, active, and stimuli-responsive targeting mechanisms has further improved the precision of nanoparticle-mediated drug delivery, reducing off-target effects and enhancing therapeutic efficacy. The use of specific ligands, including antibodies, peptides, aptamers, and small molecules, has enabled receptor-mediated targeting for a variety of biomedical applications. These advancements have demonstrated considerable promise in cancer therapy, neurological disorders, gene delivery, vaccine development, and other emerging areas of medicine. Despite substantial progress, several challenges related to biological interactions, large-scale manufacturing, long-term safety, and clinical translation remain to be addressed. A better understanding of the nano–bio interface, together with standardized production methods and regulatory frameworks, will be essential for the successful implementation of these technologies in clinical practice.





WISELEAF SCIENTIFIC VENTURES

Future developments in precision nanomedicine are expected to focus on smart, multifunctional, and personalized nanoparticle systems capable of integrating targeted drug delivery with diagnostic and therapeutic functions. Continued advances in surface engineering and nanotechnology will contribute to the development of safer, more effective, and clinically translatable nanomedicines, ultimately improving patient care and expanding the scope of modern therapeutics.

References

1. Mitchell MJ, Billingsley MM, Haley RM, Wechsler ME, Peppas NA, Langer R. Engineering precision nanoparticles for drug delivery. *Nature reviews drug discovery*. 2021 Feb;20(2):101-24.
2. Shi J, Kantoff PW, Wooster R, Farokhzad OC. Cancer nanomedicine: progress, challenges and opportunities. *Nature reviews cancer*. 2017 Jan;17(1):20-37.
3. Yoo JW, Irvine DJ, Discher DE, Mitragotri S. Bio-inspired, bioengineered and biomimetic drug delivery carriers. *Nature reviews Drug discovery*. 2011 Jul;10(7):521-35.
4. Wilhelm S, Tavares AJ, Dai Q, Ohta S, Audet J, Dvorak HF, Chan WC. Analysis of nanoparticle delivery to tumours. *Nature reviews materials*. 2016 Apr 26;1(5):16014.
5. Jadhav SP, Ahire SM, Shewale VV, Patil CD, Pagar RY, Sonawane DD, Mahajan SK. Formulation of Tablet of Nifedipine co-crystal for enhancement of solubility and other physical properties. *Biotech Res Asia*. 2025 Mar 25;22(1):191-200.
6. Etheridge ML, Campbell SA, Erdman AG, Haynes CL, Wolf SM, McCullough J. The big picture on nanomedicine: the state of investigational and approved nanomedicine products. *Nanomedicine: nanotechnology, biology and medicine*. 2013 Jan 1;9(1):1-4.
7. Pelaz B, del Pino P, Maffre P, Hartmann R, Gallego M, Rivera-Fernandez S, de la Fuente JM, Nienhaus GU, Parak WJ. Surface functionalization of nanoparticles with polyethylene glycol: effects on protein adsorption and cellular uptake. *ACS nano*. 2015 Jul 28;9(7):6996-7008.
8. Salvati A, Pitek AS, Monopoli MP, Prapainop K, Bombelli FB, Hristov DR, Kelly PM, Åberg C, Mahon E, Dawson KA. Transferrin-functionalized nanoparticles lose their





WISELEAF SCIENTIFIC VENTURES

- targeting capabilities when a biomolecule corona adsorbs on the surface. *Nature nanotechnology*. 2013 Feb;8(2):137-43.
9. Parodi A, Quattrocchi N, Van De Ven AL, Chiappini C, Evangelopoulos M, Martinez JO, Brown BS, Khaled SZ, Yazdi IK, Enzo MV, Isenhardt L. Synthetic nanoparticles functionalized with biomimetic leukocyte membranes possess cell-like functions. *Nature nanotechnology*. 2013 Jan;8(1):61-8.
 10. Decuzzi P, Ferrari M. The receptor-mediated endocytosis of nonspherical particles. *Biophysical journal*. 2008 May 15;94(10):3790-7.
 11. Honary S, Zahir F. Effect of zeta potential on the properties of nano-drug delivery systems-a review (Part 2). *Tropical journal of pharmaceutical research*. 2013 May 9;12(2):265-73.
 12. Alexis F, Pridgen E, Molnar LK, Farokhzad OC. Factors affecting the clearance and biodistribution of polymeric nanoparticles. *Molecular pharmaceutics*. 2008 Aug 4;5(4):505-15.
 13. Ahire SM, Pawar PS, Shewale VV, Jadhav SP, Mahajan SK. Magnetic Particles for Targeted Drug Delivery and Biomedical Applications.
 14. Caracciolo G, Farokhzad OC, Mahmoudi M. Biological identity of nanoparticles in vivo: clinical implications of the protein corona. *Trends in biotechnology*. 2017 Mar 1;35(3):257-64.
 15. Blanco E, Shen H, Ferrari M. Principles of nanoparticle design for overcoming biological barriers to drug delivery. *Nature biotechnology*. 2015 Sep;33(9):941-51.
 16. Wilhelm S, Tavares AJ, Dai Q, Ohta S, Audet J, Dvorak HF, Chan WC. Analysis of nanoparticle delivery to tumours. *Nature reviews materials*. 2016 Apr 26;1(5):16014.
 17. Pissuwan D, Cortie CH, Valenzuela SM, Cortie MB. Functionalised gold nanoparticles for controlling pathogenic bacteria. *Trends in biotechnology*. 2010 Apr 1;28(4):207-13.
 18. Decher G. Fuzzy nanoassemblies: toward layered polymeric multicomposites. *science*. 1997 Aug 29;277(5330):1232-7.
 19. Ahire SM, Pawar PS, Sonawane VN, Jadhav SP. Personalized Medicine and Pharmacogenomics: Impact of Genetic variation on Drug Response and Individualized





WISELEAF SCIENTIFIC VENTURES

- Therapy-A Review. *Asian Journal of Pharmacy and Technology*. 2026 Jan 27;16(1):91-8.
20. Knop K, Hoogenboom R, Fischer D, Schubert US. Poly (ethylene glycol) in drug delivery: pros and cons as well as potential alternatives. *Angewandte chemie international edition*. 2010 Aug 23;49(36):6288-308.
21. Fang RH, Kroll AV, Zhang L. Nanoparticle-based manipulation of antigen-presenting cells for cancer immunotherapy. *Small*. 2015 Nov;11(41):5483-96.
22. Pawar PS, Ahire SM, Shewale VV, Jadhav S, Mahajan SK. Nanotechnology in herbal medicines: a review. *J Hosp Pharmacy*. 2025;20(1 Suppl 3):1-9.
23. Maeda H, Bharate GY, Daruwalla J. Polymeric drugs for efficient tumor-targeted drug delivery based on EPR-effect. *European journal of pharmaceutics and biopharmaceutics*. 2009 Mar 1;71(3):409-19.
24. Sun Q, Zhou Z, Qiu N, Shen Y. Rational design of cancer nanomedicine: nanoproperty integration and synchronization. *Advanced materials*. 2017 Apr;29(14):1606628.
25. Byrne JD, Betancourt T, Brannon-Peppas L. Active targeting schemes for nanoparticle systems in cancer therapeutics. *Advanced drug delivery reviews*. 2008 Dec 14;60(15):1615-26.
26. Jadhav SP, Ahire SM, Chitte NR, Pawar PS, Sonawane I, Shewale V. Crossing the Blood–Brain Barrier: Challenges, Strategies and Emerging Technologies. *Asian Journal of Research in Pharmaceutical Sciences*. 2026 Jul;16(3):234-42.
27. Saraiva C, Praça C, Ferreira R, Santos T, Ferreira L, Bernardino L. Nanoparticle-mediated brain drug delivery: Overcoming blood–brain barrier to treat neurodegenerative diseases. *Journal of controlled release*. 2016 Aug 10;235:34-47.
28. Mura S, Couvreur P. Nanotheranostics for personalized medicine. *Advanced drug delivery reviews*. 2012 Oct 1;64(13):1394-416.
29. Germain M, Caputo F, Metcalfe S, Tosi G, Spring K, Åslund AK, Pottier A, Schiffelers R, Ceccaldi A, Schmid R. Delivering the power of nanomedicine to patients today. *Journal of Controlled Release*. 2020 Oct 10;326:164-71.





WISELEAF SCIENTIFIC VENTURES

30. Mahmoudi M, Bertrand N, Zope H, Farokhzad OC. Emerging understanding of the protein corona at the nano-bio interfaces. *Nano Today*. 2016 Dec 1;11(6):817-32.

