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NANOPARTICLE MEDIATED DRUG DELIVERY SYSTEMS FOR CANCER TREATMENT

Chapter 12: Future Prospects and Emerging Trends in Cancer Nanomedicine

Dr. Chandrashekhar D. Patil¹, Mr. Vitthal B. Kundgir², Mr. Vijay V. Shewale³,

*¹Associate Professor, Department of Pharmacology, Divine College of Pharmacy, Satana,
Nashik, Maharashtra.*

*²Lecturer, Department of Pharmacology, Divine College of Pharmacy, Satana, Nashik,
Maharashtra.*

*³Assistant Professor, Department of Pharmacognosy, Divine College of Pharmacy, Satana,
Nashik, Maharashtra.*

Abstract

Cancer nanomedicine has emerged as a promising strategy for improving the selectivity, therapeutic efficacy, and safety of anticancer interventions. Conventional cancer treatments are often limited by non-specific drug distribution, systemic toxicity, multidrug resistance, and inadequate drug accumulation at tumor sites. Nanoparticle-based drug delivery systems offer opportunities to overcome these limitations through controlled drug release, enhanced tumor targeting, improved pharmacokinetic behavior, and the simultaneous delivery of multiple therapeutic agents. The future of cancer nanomedicine is increasingly focused on the development of intelligent, multifunctional, and patient-specific nanocarriers capable of responding to biological and pathological stimuli within the tumor microenvironment. Emerging platforms, including biomimetic nanoparticles, cell membrane-coated systems, exosome-inspired nanocarriers, biodegradable nanomaterials, and hybrid nanosystems, are expanding the therapeutic potential of nanotechnology. The integration of nanomedicine with artificial intelligence, machine learning, genomics, immunotherapy, gene therapy, and advanced imaging is expected to facilitate the rational design of precision drug delivery systems and improve treatment personalization. Furthermore, theranostic nanoparticles capable of integrating diagnosis and therapy may support real-time monitoring of disease progression





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and therapeutic response. Despite substantial progress, challenges related to biological heterogeneity, nanoparticle safety, large-scale manufacturing, reproducibility, regulatory evaluation, and clinical translation remain significant. Future advances will require interdisciplinary approaches that integrate pharmaceutical sciences, materials engineering, computational technologies, and clinical oncology. This chapter discusses the emerging trends, technological innovations, translational challenges, and future opportunities shaping the next generation of cancer nanomedicine, with particular emphasis on intelligent, personalized, and clinically relevant nanoparticle-mediated drug delivery systems.

keywords: Cancer nanomedicine; Nanoparticle-mediated drug delivery; Precision oncology; Artificial intelligence; Smart nanocarriers; Theranostics; Clinical translation.

1. Introduction

Cancer remains one of the most challenging global health problems, characterized by uncontrolled cellular proliferation, progressive tissue invasion, metastatic dissemination, and substantial molecular heterogeneity. Although conventional therapeutic modalities, including chemotherapy, radiotherapy, surgery, targeted therapy, and immunotherapy, have significantly improved clinical outcomes, their effectiveness is frequently restricted by nonspecific drug distribution, dose-limiting toxicity, multidrug resistance, inadequate accumulation at tumor sites, and interpatient variability in therapeutic response[1]. These limitations have stimulated the development of advanced drug-delivery technologies capable of improving the spatial and temporal control of anticancer therapeutics while minimizing systemic adverse effects [2].

Nanomedicine has emerged as an important component of modern cancer therapeutics by exploiting nanoscale materials as carriers for chemotherapeutic agents, nucleic acids, proteins, imaging agents, and combination therapies. Nanoparticle-mediated drug delivery can modify the physicochemical and pharmacokinetic characteristics of therapeutic molecules, improve their aqueous solubility and stability, facilitate controlled or sustained release, and enhance delivery to selected biological compartments. In addition, nanoscale systems can be engineered with surface ligands, antibodies, peptides, aptamers, or biomimetic components to improve tumor-associated recognition. These characteristics have established nanocarriers as a versatile





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platform for addressing several limitations associated with conventional cancer treatment [3-4].

The field of cancer nanomedicine has progressively evolved from relatively simple drug-encapsulation systems toward sophisticated multifunctional and biologically responsive platforms. Early approaches primarily focused on improving drug solubility, circulation time, and passive accumulation within tumors. Subsequent advances introduced active targeting, controlled drug release, stimulus-responsive systems, and multifunctional nanocarriers capable of simultaneously delivering therapeutic and diagnostic agents. More recent developments have incorporated biomimetic materials, cell-derived vesicles, nucleic-acid therapeutics, immunomodulatory agents, and tumor-microenvironment-responsive mechanisms. Consequently, contemporary cancer nanomedicine increasingly emphasizes biological precision, therapeutic personalization, and integration of multiple treatment modalities within a single nanoscale platform [5].

A particularly important emerging direction is the convergence of nanotechnology with precision medicine. Tumors differ substantially between patients in their genetic profile, molecular characteristics, receptor expression, immune landscape, vascular architecture, and tumor-microenvironmental conditions. Therefore, a universal nanocarrier may not provide equivalent therapeutic benefits across different patient populations. Integration of genomic, transcriptomic, proteomic, and imaging information with nanomedicine may facilitate the selection of appropriate therapeutic targets, optimization of drug combinations, and development of patient-specific delivery systems. Biomarker-guided nanotherapeutics may consequently improve treatment selectivity and reduce unnecessary exposure of healthy tissues.

Artificial intelligence (AI) and machine learning (ML) are also transforming the design and optimization of cancer nanomedicines. Conventional formulation development often involves extensive experimental screening of materials, compositions, particle sizes, surface characteristics, drug-loading conditions, and release parameters. AI-based approaches can analyze complex multidimensional datasets to identify relationships between formulation attributes and biological outcomes. Such computational approaches have potential applications





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in nanoparticle design, prediction of drug-carrier interactions, formulation optimization, toxicity assessment, pharmacokinetic modeling, and prediction of therapeutic responses. The integration of AI with nanomedicine may therefore accelerate the transition from empirical formulation development toward data-driven and predictive nanotherapeutics [6].

Another major area of future development involves the use of nanoparticles for delivering biological therapeutics that are otherwise difficult to administer effectively. Nucleic-acid-based therapeutics, including messenger RNA (mRNA), small interfering RNA (siRNA), microRNA, antisense oligonucleotides, and genome-editing components, require efficient protection from enzymatic degradation and intracellular delivery. Nanocarriers can facilitate their transport through biological barriers and promote cellular uptake and intracellular release. In parallel, nanoparticle-enabled immunotherapy, photothermal therapy, photodynamic therapy, and nanotheranostic systems are expanding the therapeutic potential of cancer nanomedicine by combining drug delivery with immune modulation, energy-based treatment, molecular imaging, and disease monitoring.

Despite substantial scientific progress, the translation of promising nanomedicines from laboratory research to routine clinical application remains challenging. Nanoparticle physicochemical characteristics can strongly influence absorption, distribution, metabolism, elimination, immune recognition, toxicity, and therapeutic performance. Differences in particle size, morphology, surface chemistry, drug-loading efficiency, manufacturing processes, and storage conditions may affect reproducibility and clinical outcomes. Furthermore, complex nanomedicines may present challenges in large-scale manufacturing, quality control, regulatory evaluation, cost-effectiveness, and long-term safety assessment. Addressing these issues is essential for transforming innovative nanosystems from experimental platforms into reliable and clinically accessible therapeutic products [7-10].





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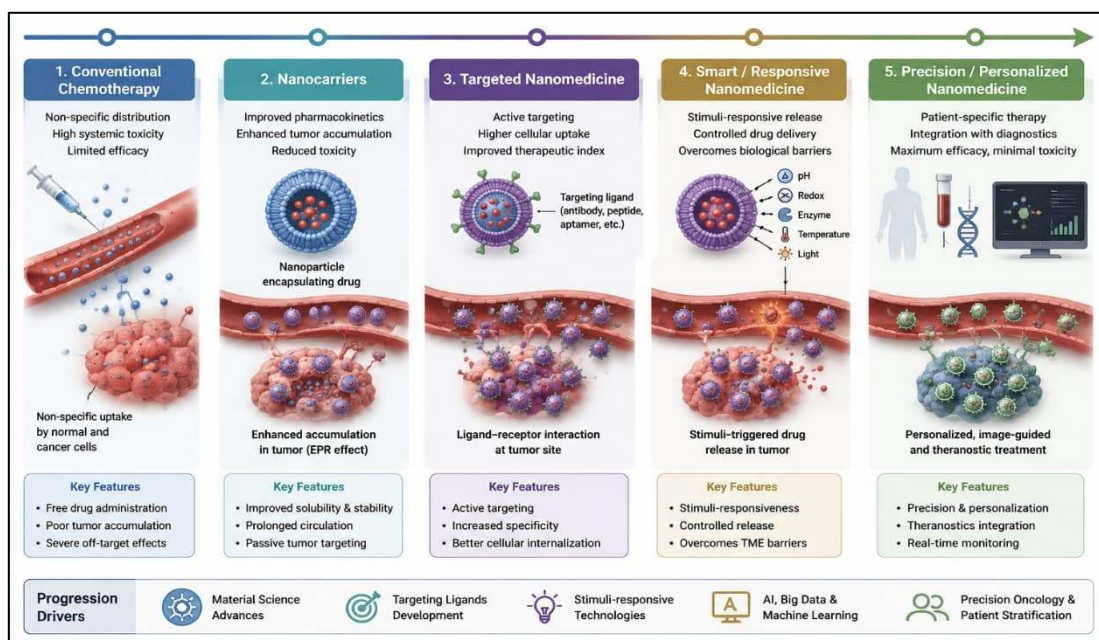


Fig.1 Evolution of Cancer Nanomedicine

2. Evolution and Current Status of Cancer Nanomedicine

Cancer nanomedicine has evolved from simple nanoscale drug carriers to advanced systems capable of targeted, controlled, and biologically responsive drug delivery. Nanoparticles offer advantages such as high surface area, tunable surface properties, improved drug solubility, protection of therapeutic molecules, and modified pharmacokinetic behavior. These properties have supported their application in improving the therapeutic performance of anticancer agents.

2.1 Early Development of Cancer Nanomedicine

Early nanomedicine research focused mainly on overcoming limitations of conventional anticancer drugs, including poor solubility, rapid elimination, nonspecific distribution, and systemic toxicity. Liposomes, polymeric nanoparticles, micelles, and other colloidal systems were developed to improve drug stability, encapsulation, and controlled release. The clinical development of liposomal anticancer formulations demonstrated that nanocarriers could modify drug distribution and improve treatment tolerability, establishing an important foundation for modern cancer nanomedicine [11].

2.2 Transition to Targeted Nanomedicine

Research subsequently shifted toward improving tumor localization. Passive targeting was associated with the enhanced permeability and retention (EPR) effect, while surface





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modification with polymers such as PEG was used to prolong circulation. Active targeting further advanced the field through the incorporation of antibodies, peptides, aptamers, and other ligands that recognize tumor-associated receptors. These approaches primarily aim to improve cellular uptake and intracellular delivery [12].

2.3 Multifunctional and Stimuli-Responsive Systems

Modern nanomedicine increasingly incorporates stimuli-responsive mechanisms. Nanoparticles can respond to tumor-associated pH, enzymes, redox conditions, hypoxia, temperature, light, ultrasound, or magnetic fields to control drug release. These systems provide greater spatial and temporal control over therapeutic delivery and can combine multiple functions such as targeting, therapy, imaging, and controlled release [13].

2.4 Emergence of Nanotheranostics

Nanotheranostics combine diagnostic and therapeutic functions within a single nano system. Such platforms may incorporate imaging agents together with anticancer drugs, enabling tumor visualization, drug delivery, and treatment monitoring. This approach has particular relevance to precision oncology [14].

2.5 Integration with Biological Therapeutics

The application of nanotechnology has expanded beyond conventional chemotherapy to include siRNA, mRNA, microRNA, proteins, gene-editing components, and Immunotherapeutics. Nanocarriers can protect these sensitive molecules from degradation and facilitate their delivery into target cells. Nanoparticle-based immunotherapy is also being investigated to improve immune activation and enable combination treatment with other anticancer approaches.

2.6 Current Status and Challenges

Several nanoparticle-based formulations have reached clinical application, demonstrating the practical potential of nanomedicine. However, many promising systems remain at preclinical or early clinical stages. Major challenges include tumor heterogeneity, variable biodistribution, Nano toxicity, limited tissue penetration, manufacturing complexity, reproducibility, and regulatory requirements. Current research therefore emphasizes biologically informed nanoparticle design rather than relying solely on nanoscale size or passive tumor accumulation.





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3 Next-Generation Nanoparticle Platforms

Next-generation nanoparticle platforms represent an important advancement in cancer nanomedicine. Unlike conventional nanocarriers that mainly improve drug solubility, stability, and circulation, newer systems are designed to provide precise targeting, controlled drug release, tumor-responsive behavior, and multiple therapeutic functions. These platforms aim to overcome biological barriers such as tumor heterogeneity, poor tissue penetration, rapid clearance, and nonspecific drug distribution [15].

3.1 Smart Nanoparticles

Smart nanoparticles are specially engineered nanocarriers that can respond to specific biological or external stimuli and modify their behavior accordingly. Their major objective is to deliver therapeutic agents at the appropriate site and time while minimizing unwanted exposure to healthy tissues. Tumors possess several unique characteristics, including acidic pH, altered redox conditions, hypoxia, increased enzyme activity, and abnormal vascular properties. These characteristics can be utilized as triggers for smart nanoparticle systems. External stimuli such as light, ultrasound, magnetic fields, and temperature can also be applied to control nanoparticle activity. Smart nanoparticles may perform several functions simultaneously, including tumor targeting, controlled drug release, imaging, and therapeutic activation. For example, a nanoparticle may remain stable during circulation but release its drug after reaching an acidic tumor environment. Such systems provide improved spatial and temporal control over drug delivery.

However, increasing the functional complexity of smart nanoparticles may create challenges related to formulation stability, manufacturing, reproducibility, toxicity, and regulatory approval. Therefore, future development should focus on achieving effective therapeutic responses with relatively simple and clinically practical designs.

3.2 Stimuli-Responsive Nanocarriers

Stimuli-responsive nanocarriers are designed to release their therapeutic payload in response to specific endogenous or exogenous stimuli. These systems are particularly valuable in cancer therapy because the tumor microenvironment differs from normal tissues in several physicochemical and biological characteristics. Endogenous stimuli include acidic pH,





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enzymes, redox conditions, reactive oxygen species, and hypoxia. pH-responsive nanoparticles can release drugs under acidic tumor or intracellular conditions. Redox-responsive systems may use chemical linkages that are cleaved under intracellular reducing conditions. Enzyme-responsive nanoparticles can exploit enzymes that are overexpressed in certain tumors to trigger drug release. Exogenous stimuli include light, ultrasound, magnetic fields, and temperature. Light-responsive systems can provide localized activation, while magnetic nanoparticles can be manipulated using external magnetic fields. Thermoresponsive systems can release drugs following localized temperature changes[16].

The use of multiple stimuli in a single formulation is another emerging approach. For example, a nanoparticle may respond first to tumor acidity and subsequently to intracellular redox conditions. This sequential response can improve drug-release specificity. Nevertheless, multi-stimuli systems may require more complex manufacturing and characterization.

3.3 Biomimetic Nanoparticles

Biomimetic nanoparticles are designed to imitate selected properties of natural biological systems. They combine the advantages of engineered nanomaterials with biological components such as cell membranes, proteins, peptides, or extracellular-vesicle-inspired structures. Cell membrane-coated nanoparticles are an important example. Membranes obtained from erythrocytes, platelets, immune cells, or cancer cells can be incorporated around nanoparticle cores. These biological coatings may improve circulation, reduce immune recognition, and promote interaction with specific cells or tissues.

Cancer-cell membrane-coated nanoparticles are being investigated because tumor-derived membrane components may facilitate recognition of similar cancer cells. Similarly, platelet- and immune-cell-derived membranes may provide opportunities for interaction with tumor-associated components. Exosome-inspired systems represent another promising biomimetic approach. Exosomes naturally participate in intercellular communication and can transport biological molecules between cells. Their properties have therefore inspired the development of nanocarriers for drug and nucleic-acid delivery. Despite their potential, biomimetic nanoparticles face challenges involving biological-source variability, membrane isolation,





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stability, purification, reproducibility, and large-scale production. Standardized manufacturing and characterization will be essential for future clinical translation.

3.4 Hybrid and Multifunctional Nanoparticles

Hybrid nanoparticles combine two or more different materials or functional components in a single delivery system. Examples include combinations of lipidic, polymeric, inorganic, metallic, and biological materials. The objective is to combine the advantages of individual components while minimizing their limitations. Multifunctional nanoparticles can simultaneously provide drug delivery, targeting, imaging, and therapeutic activity. For example, one nanoparticle may contain a chemotherapeutic agent along with an imaging component and a targeting ligand. Other systems may combine chemotherapy with gene therapy, photothermal therapy, photodynamic therapy, or immunotherapy.

These platforms are particularly relevant to combination cancer therapy, where multiple therapeutic mechanisms may be required to overcome drug resistance and tumor heterogeneity. Integration of diagnostic and therapeutic functions also forms the basis of nano theranostics, allowing treatment and disease monitoring to be performed using a common platform. However, multifunctionality increases formulation complexity. Each additional component may influence particle stability, pharmacokinetics, toxicity, manufacturing, and regulatory assessment. Therefore, multifunctional nanoparticles should be developed using a rational design approach in which every component has a clearly defined therapeutic or diagnostic purpose[17].

4. Personalized and Precision Nanomedicine

Personalized and precision nanomedicine represents a transition from population-based cancer treatment toward therapeutic strategies based on the molecular, genetic, phenotypic, and clinical characteristics of individual patients. Conventional anticancer therapy often follows standardized protocols; however, interpatient and intratumoral heterogeneity can produce different therapeutic responses and toxicity profiles. Nanotechnology provides a flexible platform in which nanoparticle composition, size, surface chemistry, targeting ligands, drug combinations, and release mechanisms can be modified according to specific biological requirements. The integration of molecular profiling, biomarker identification, multi-omics





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technologies, advanced imaging, and computational analysis with nanocarrier engineering provides opportunities to match therapeutic payloads and delivery systems with individual tumor characteristics. This approach may improve tumor selectivity, intracellular drug delivery, reduce systemic exposure, and facilitate treatment adaptation as disease evolves[18].

4.1 Patient-Specific Nano therapeutics

Patient-specific Nano therapeutics are designed according to the biological characteristics of an individual tumor. Important factors include tumor type and stage, receptor expression, mutational profile, immune status, vascular characteristics, extracellular matrix composition, and previous treatment exposure. These factors can influence nanoparticle accumulation, cellular uptake, drug release, and therapeutic response.

The development of patient-specific Nano therapeutics involves collecting clinical and molecular information through tissue biopsy, imaging, circulating biomarkers, or liquid biopsy. This information can help identify molecular targets and therapeutic vulnerabilities, followed by selection of an appropriate nanoparticle and therapeutic payload. Nanocarriers are particularly useful for delivering biologically complex therapeutics such as siRNA, proteins, antibodies, and other biopharmaceuticals, which may otherwise face degradation and cellular barriers[19].

However, individualized nanoparticle manufacturing remains challenging because each formulation must meet strict requirements for quality, stability, safety, and reproducibility. Therefore, modular nanoplatfroms, in which targeting ligands or therapeutic payloads can be rapidly changed, may provide a more practical approach.

4.2 Biomarker-Guided Targeting

Biomarker-guided targeting is an important component of precision nanomedicine because the effectiveness of targeted nanoparticles depends on the presence of suitable molecular targets. Cancer biomarkers may include cell-surface receptors, tumor-associated antigens, genetic alterations, enzymes, extracellular matrix components, and circulating tumor DNA. Targeting ligands such as antibodies, peptides, aptamers, and carbohydrates can be incorporated onto nanoparticle surfaces to improve recognition of specific molecular targets. Biomarker information can therefore guide the selection of both targeting ligands and therapeutic





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payloads. Targeting is not limited to cancer cells. The tumor microenvironment contains endothelial cells, fibroblasts, macrophages, lymphocytes, and extracellular matrix components, which may also contribute to tumor progression and treatment resistance. Biomarkers can additionally support treatment monitoring. Liquid-biopsy markers such as circulating tumor DNA may provide information regarding treatment response, resistance, and disease progression. However, biomarker expression can vary between patients, tumor regions, and metastatic sites. Therefore, future precision nanomedicine may require dynamic biomarker assessment rather than dependence on a single static target.

4.3 Integration of Genomics and Proteomics

Genomics and proteomics provide complementary information about cancer biology. Genomic analysis identifies mutations and other genetic alterations, whereas proteomics provides information regarding protein expression, signaling pathways, and functional cellular states. Integrating these data with nanomedicine can improve individualized therapeutic design. Genomic profiling can identify molecular alterations associated with oncogenic pathways, drug resistance, and tumor-specific targets. Such information can guide therapeutic selection, while nanoparticle encapsulation may improve drug delivery and reduce nonspecific exposure. Proteomic analysis can identify receptor expression and changes within the tumor microenvironment, supporting the selection of suitable targeting ligands. The integration of genomics, transcriptomics, proteomics, metabolomics, and other datasets forms the basis of multi-omics-guided nanomedicine.

Artificial intelligence and computational modeling can further analyze large molecular datasets to identify relationships between tumor characteristics, nanoparticle properties, and therapeutic responses. However, successful implementation requires standardized datasets, reliable biomarkers, robust bioinformatics, and clinically validated predictive models.

4.4 Personalized Dosing and Drug Delivery

Personalized dosing is another important aspect of precision nanomedicine. Conventional dosing commonly considers body weight, body-surface area, renal and hepatic function, and population-based pharmacokinetic parameters. These approaches may not fully account for differences in tumor biology, nanoparticle clearance, immune interactions, and tissue





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distribution. Nanoparticles can alter the circulation time, biodistribution, cellular uptake, and drug-release profile of therapeutic agents. Therefore, personalized treatment should consider both the therapeutic dose and the biological behavior of the nanocarrier.

Pharmacokinetic and pharmacodynamic modeling can help integrate patient characteristics with drug concentration and response data. An emerging concept is adaptive dosing, where treatment is modified according to individual therapeutic response. Imaging, circulating tumor DNA, and molecular biomarkers may provide feedback for treatment adjustment. The route of administration can also be selected according to tumor location and disease characteristics. Intravenous delivery is widely used for systemic treatment, whereas local or regional administration may be considered when anatomically appropriate.

5. Artificial Intelligence and Machine Learning in Cancer Nanomedicine

The integration of artificial intelligence (AI), machine learning (ML), and nanotechnology is establishing a data-driven approach to the design, optimization, characterization, and clinical development of cancer nanomedicines. Conventional nanoparticle development often depends on repeated experimentation, while nanoparticle performance is influenced by numerous variables such as particle size, morphology, surface charge, composition, drug loading, release kinetics, stability, biodistribution, and cellular uptake. AI and ML can analyze these multidimensional datasets and identify relationships that may be difficult to determine experimentally. AI is increasingly being applied throughout the nanomedicine development pipeline, including nanoparticle design, formulation optimization, prediction of nano–bio interactions, pharmacokinetic behavior, therapeutic efficacy, and toxicity. This is particularly relevant to precision oncology because both nanoparticle properties and tumor biology show considerable variability. However, AI should currently be considered a complementary decision-support tool rather than a replacement for experimental and clinical validation [20].

5.1 AI-Assisted Nanoparticle Design

Designing effective nanoparticles requires optimization of particle size, morphology, surface charge, composition, ligand density, drug-loading capacity, stability, and release characteristics. Conventional optimization may require extensive experimental screening. ML models can use previous formulation and experimental data to establish relationships between





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formulation variables and desired nanoparticle properties. These models can predict particle size, encapsulation efficiency, stability, and biological performance and help prioritize promising formulations for experimental testing. AI can also support the selection of targeting ligands by analyzing relationships between nanoparticle surface characteristics and biological receptors. Advanced models may integrate molecular structures, imaging data, omics information, and nanoparticle characteristics to support tumor-specific nanocarrier design. However, predictive performance depends strongly on the quality and diversity of available datasets[21].

5.2 Prediction of Drug-Nanocarrier Interactions

Drug–nanocarrier interactions influence drug loading, formulation stability, release behavior, and therapeutic performance. Drug properties such as molecular size, polarity, charge, hydrophobicity, and ionization can affect interactions with different Nanocarrier materials.

AI and ML can model these relationships using molecular descriptors and experimental data to predict encapsulation efficiency, drug loading, release behavior, and stability. This can reduce the number of drugs–carrier combinations requiring experimental evaluation. AI can also help study nanoparticle interactions with plasma proteins. After administration, nanoparticles rapidly acquire a protein corona, which can influence immune recognition, biodistribution, cellular uptake, and toxicity. Computational modeling may help predict these interactions and improve nanoparticle design. Nevertheless, computational predictions may differ from biological behavior after administration because of protein adsorption, enzymatic degradation, immune responses, and tissue-specific conditions. Experimental validation therefore remains essential.

5.3 AI-Driven Formulation Optimization

Formulation optimization is one of the most practical applications of ML in pharmaceutical nanotechnology. Nanoparticle composition and processing conditions can strongly influence particle size, polydispersity, zeta potential, drug loading, release, and stability. ML can identify linear and nonlinear relationships between formulation variables and critical quality attributes. Predictive models can therefore help identify optimal formulation regions while reducing experimental workload. AI can also support multi-objective optimization, where high drug





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loading, controlled release, stability, efficient cellular uptake, and low toxicity must be achieved simultaneously. Process parameters such as mixing rate, temperature, solvent composition, and processing time can also be analyzed to identify suitable manufacturing conditions.

However, AI-generated formulations require experimental confirmation because statistical correlations do not necessarily establish mechanistic relationships. Independent validation is essential before practical application [22].

5.4 Prediction of Therapeutic Response

AI and ML are increasingly being investigated for predicting the biological performance of cancer nanomedicine. Treatment response depends on tumor genotype, receptor expression, immune status, tumor microenvironment, nanoparticle biodistribution, drug sensitivity, and patient-specific pharmacokinetics. ML models can potentially predict cellular uptake, tumor accumulation, drug release, cytotoxicity, and therapeutic efficacy. Molecular and imaging data may also be integrated to identify patient groups that are more likely to respond to specific nanotherapeutics. Another emerging application is prediction of treatment resistance. AI models may identify molecular patterns associated with resistance and support selection of alternative drug combinations. Image-based AI can also assist in evaluating tumor characteristics, nanoparticle distribution, and treatment-related changes.

However, therapeutic-response prediction is more complex than predicting physicochemical properties. Biological datasets are often limited and heterogeneous, making external validation and prospective evaluation necessary.

5.5 Integration of AI with Precision Cancer Nanomedicine

The greatest potential of AI may arise from combining nanoparticle formulation data with patient-specific molecular and clinical information. A computational framework could integrate nanoparticle properties, tumor molecular profiles, imaging data, pharmacokinetics, treatment history, and clinical outcomes. This approach could support a sequential workflow in which patient data identify therapeutic targets, AI predicts suitable nanocarriers, formulations are experimentally optimized, and clinical results are used to improve future predictions. Such integration may contribute to more individualized and adaptive cancer





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therapy. Future developments may include generative AI, reinforcement learning, digital twins, and multimodal AI models. However, these technologies remain at different stages of research and should not yet be considered established clinical practices.

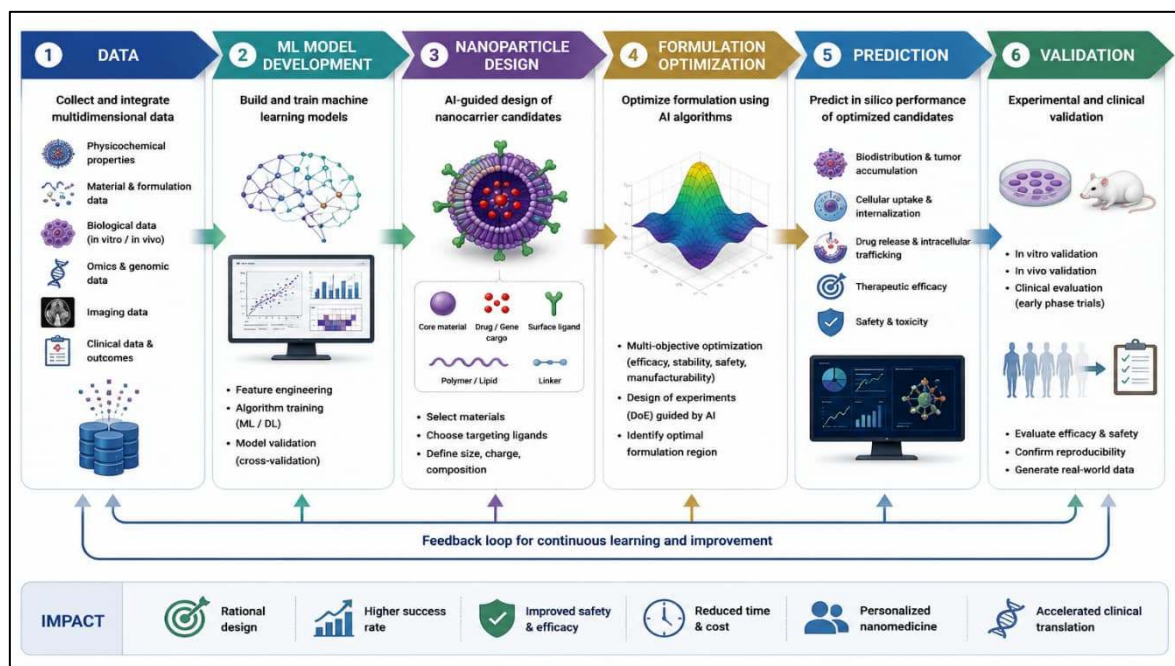


Fig.5 AI-Driven Cancer Nanomedicine Development Pipeline [22]

5.6 Challenges and Limitations

Several challenges limit the widespread application of AI in cancer nanomedicine. Data quality and availability are major concerns because nanomedicine datasets are often limited, heterogeneous, and generated using different experimental methods. Model interpretability is also important, particularly in pharmaceutical development where biological mechanisms and safety must be understood. Overfitting, algorithmic bias, and limited generalizability may occur when models are trained on narrow datasets. Regulatory acceptance represents another challenge. AI-based predictions used in formulation development or clinical decision-making require appropriate validation and documentation. Standardized data reporting, transparent algorithms, and rigorous experimental validation are therefore essential.

6 Emerging Nanotechnology-Based Therapeutic Approaches





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The integration of nanotechnology with molecular biology, gene therapy, immunology, and advanced diagnostic techniques has expanded the therapeutic potential of cancer nanomedicine beyond conventional chemotherapy. Nanoparticles can act as drug carriers, targeting systems, intracellular delivery vehicles, and therapeutic agents. Their physicochemical properties can be modified to improve drug stability, bioavailability, cellular uptake, controlled release, and tumor localization. Emerging approaches therefore focus on gene and RNA delivery, mRNA therapeutics, CRISPR/Cas systems, immunotherapy, phototherapy, and nano theranostics [23].

6.1 Nanocarrier-Mediated Gene and RNA Delivery

Gene and RNA therapeutics offer opportunities to regulate molecular pathways involved in cancer progression. Therapeutic nucleic acids include siRNA, miRNA, mRNA, antisense oligonucleotides, and DNA. However, their clinical application is limited by enzymatic degradation, poor stability, unfavorable pharmacokinetics, and inefficient cellular entry. Nanocarriers such as lipid nanoparticles, polymeric nanoparticles, dendrimers, and hybrid systems can protect nucleic acids and facilitate intracellular delivery. Nanoparticle-mediated siRNA delivery can suppress genes associated with proliferation, angiogenesis, metastasis, and drug resistance. Co-delivery of RNA therapeutics with anticancer drugs is also being investigated to simultaneously target tumor growth and resistance mechanisms.

6.2 mRNA Therapeutics

mRNA-based nanomedicine is an emerging approach for cancer vaccination and immune modulation. mRNA can encode tumor antigens, tumor-suppressor proteins, cytokines, or other therapeutic molecules. Lipid nanoparticles are particularly useful because they protect mRNA from degradation and facilitate cellular uptake. Personalized mRNA cancer vaccines may be developed using tumor sequencing to identify patient-specific neoantigens. However, mRNA stability, tissue-selective delivery, innate immune activation, and manufacturing consistency remain important challenges.

6.3 CRISPR/Cas-Based Nano delivery

CRISPR/Cas technology enables targeted modification of specific genetic sequences. Nanoparticles can deliver Cas proteins, guide RNA, or Cas-encoding mRNA to cancer cells. This approach may be useful for targeting oncogenes, modifying immune cells, and





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investigating mechanisms of drug resistance. Nevertheless, delivery efficiency, off-target editing, immune responses, and control of genome-editing activity require careful evaluation.

6.4 Nanoparticle-Enabled Immunotherapy

Nanoparticles can enhance cancer immunotherapy by delivering tumor antigens, adjuvants, cytokines, immune checkpoint modulators, and nucleic acids. Controlled delivery can improve immune activation while reducing systemic exposure. Nanoparticles can also be designed to modify immunosuppressive components of the tumor microenvironment. Combining nanocarriers with chemotherapy, phototherapy, or immunotherapy may further enhance antitumor responses.

6.5 Photothermal and Photodynamic Therapy

Photothermal therapy (PTT) uses nanoparticles to convert light energy into localized heat, whereas photodynamic therapy (PDT) generates reactive oxygen species following light activation. Gold, carbon-based, and other nanomaterials have been investigated for PTT, while nanoparticles can improve the delivery of photosensitizers for PDT. Combining phototherapy with chemotherapy or immunotherapy may overcome some therapeutic limitations.

6.6 Nano theranostics

Nano theranostics combines diagnostic imaging and therapeutic functions within a single nanoparticle platform. These systems may incorporate imaging agents together with anticancer drugs, targeting ligands, or therapeutic components. They can potentially support tumor visualization, image-guided delivery, and treatment-response monitoring. Overall, emerging nanotechnology-based approaches are transforming nanoparticles into multifunctional platforms for targeted and personalized cancer therapy. However, safety, biological variability, manufacturing, scalability, and clinical validation remain essential for successful translation [24-26].

7 Advanced Tumor-Targeting Strategies

Effective cancer nanomedicine requires nanoparticles to reach the tumor, penetrate tumor tissue, interact with target cells, and release their therapeutic payload at the appropriate intracellular site. Modern targeting strategies therefore focus on overcoming sequential biological barriers rather than relying only on tumor accumulation. Tumor heterogeneity,





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abnormal vasculature, extracellular matrix, altered pH, hypoxia, and variable receptor expression strongly influence nanoparticle distribution and therapeutic response.

7.1 Active and Passive Targeting

Passive targeting mainly depends on the physicochemical properties of nanoparticles and tumor biology. The enhanced permeability and retention (EPR) effect suggests that abnormal tumor vasculature and impaired lymphatic drainage may promote nanoparticle accumulation. However, the EPR effect varies considerably among tumor types and patients. Active targeting involves functionalizing nanoparticles with antibodies, peptides, aptamers, carbohydrates, or other ligands that recognize tumor-associated receptors. Targets such as HER2, folate receptors, transferrin receptors, and integrins have been investigated. Active targeting primarily enhances cellular recognition and uptake after nanoparticles reach the tumor. Nevertheless, heterogeneous receptor expression and protein-corona formation can limit targeting efficiency.

Table 1 Comparison of Advanced Tumor-Targeting Strategies[27]

Targeting Strategy	Mechanism	Main Target	Advantage	Limitation
Passive targeting	Tumor accumulation through EPR effect	Abnormal tumor vasculature	Simple; no ligand required	Variable EPR effect
Active targeting	Ligand–receptor recognition	Tumor-cell receptors	Improved cellular uptake	Tumor heterogeneity
TME-responsive targeting	Response to pH, redox, enzymes, or hypoxia	Tumor microenvironment	Controlled drug release	Variable TME conditions
Organelle targeting	Specific intracellular localization	Nucleus, mitochondria, lysosomes	Enhanced intracellular activity	Complex design and trafficking

7.2 Tumor Microenvironment-Responsive Delivery

The tumor microenvironment (TME) provides several biological triggers for controlled drug release. pH-responsive nanoparticles can release drugs under acidic tumor or intracellular conditions. Redox-responsive systems exploit elevated intracellular glutathione, while





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enzyme-responsive systems utilize tumor-associated enzymatic activity. Hypoxia-responsive nanoparticles are designed to respond to low-oxygen conditions frequently present in solid tumors. Multi-stimuli systems can combine two or more triggers, such as pH/redox or enzyme/hypoxia responsiveness, providing improved control over drug release. However, increased complexity may affect formulation stability and manufacturing.

7.3 Multi-Stage Targeting

Multi-stage targeting recognizes that nanoparticle delivery involves several sequential steps: circulation → tumor localization → tissue penetration → cellular uptake → intracellular release. Nanoparticles can therefore be designed to change their size, surface charge, or targeting properties at different stages. For example, a nanoparticle may remain stable during circulation, expose a targeting ligand within the tumor, and subsequently release its payload after cellular internalization [28].

7.4 Organelle-Specific Drug Delivery

Targeting specific intracellular organelles can further improve therapeutic precision. Nuclear targeting is relevant to DNA and gene-based therapies, whereas mitochondrial targeting may promote apoptosis by disrupting mitochondrial function. Lysosomal targeting can influence intracellular degradation and autophagy, while endoplasmic-reticulum targeting may induce therapeutic ER stress.

8 Emerging Materials and Innovative Nanocarriers

The development of cancer nanomedicine has stimulated the exploration of advanced materials and innovative nanocarriers designed to overcome limitations of conventional systems. Current research emphasizes biodegradability, biomimicry, sustainable synthesis, self-assembly, multifunctionality, and active therapeutic delivery. These approaches aim to improve drug stability, tumor targeting, cellular uptake, controlled release, and safety.

8.1 Biodegradable Nanomaterials

Biodegradable materials such as PLGA, PLA, and PCL can gradually degrade into products that may be eliminated from the body. These materials support controlled delivery of anticancer drugs, nucleic acids, and proteins. Their degradation rate can be modified through polymer





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composition, molecular weight, and particle characteristics. However, degradation products, persistence, and premature drug release require careful evaluation.

8.2 Green Nanotechnology

Green nanotechnology focuses on environmentally sustainable nanoparticle synthesis using plants, microorganisms, enzymes, proteins, and other biological resources. Plant-derived phytochemicals can act as reducing and stabilizing agents during nanoparticle production. Although this approach can reduce chemical usage, variability in biological materials may affect particle size, morphology, composition, and therapeutic activity. Therefore, standardization and quality control remain essential[29].

8.3 Biomimetic and Exosome-Inspired Nanocarriers

Cell membrane-coated nanoparticles incorporate membranes from erythrocytes, platelets, cancer cells, or immune cells to obtain selected biological properties such as immune evasion and cellular recognition. Exosome-inspired systems similarly exploit natural mechanisms of cellular communication and uptake. These platforms show promise for drug, protein, and RNA delivery, but membrane preparation, purity, scalability, and reproducibility remain major challenges.

8.4 Self-Assembling Nanomaterials

Self-assembling systems spontaneously organize into nanostructures through molecular interactions. Peptides, lipids, polymers, and small molecules can form structures capable of controlled drug release. Tumor-responsive self-assembly may improve local retention and therapeutic activity, although physiological stability and predictable assembly remain important considerations.

8.5 Nano robotic and Hybrid Systems

Nano robotic systems are being investigated for externally guided drug delivery, sensing, and localized therapy, particularly using magnetic or acoustic mechanisms. Hybrid nanocarriers combine multiple materials or biological components to provide targeting, imaging, and multimodal therapy [30].





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9 Clinical Translation and Regulatory Perspectives

The successful translation of nanoparticle-based cancer therapies from laboratory research to clinical practice requires careful consideration of safety, pharmacokinetics, manufacturing, quality, regulatory compliance, and economic feasibility. Although nanomedicine offer improved drug delivery and therapeutic targeting, their complex physicochemical and biological characteristics can create challenges during clinical development. Therefore, translational research should integrate pharmaceutical, toxicological, clinical, manufacturing, and regulatory perspectives from the early stages of development [31].

9.1 Safety and Nanotoxicological Considerations

Nanoparticles may interact with cells, proteins, immune components, and organs differently from conventional drug molecules. Factors such as particle size, surface charge, morphology, composition, and biodegradability can influence toxicity. Potential concerns include oxidative stress, inflammation, immunological reactions, organ accumulation, and long-term persistence. Comprehensive evaluation of acute, chronic, genotoxic, immunological, and organ-specific toxicity is therefore essential before clinical application.

9.2 Pharmacokinetics and Biodistribution

Nanoparticle encapsulation can modify drug absorption, circulation time, distribution, metabolism, and elimination. Biodistribution depends on particle size, surface characteristics, composition, and interactions with biological proteins. Important parameters include tumor accumulation, tissue penetration, cellular uptake, drug release, and clearance. Understanding these factors is essential for establishing appropriate dosing and predicting therapeutic efficacy [32].

9.3 Scale-Up and Manufacturing

Laboratory-scale nanoparticle production may not directly translate to industrial manufacturing. Changes in mixing, temperature, raw materials, processing conditions, and purification can affect particle size, drug loading, stability, and release characteristics. Scalable and reproducible manufacturing processes are therefore required. Quality by Design (QbD) and process optimization can help maintain consistent product quality during scale-up.





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9.4 Reproducibility and Quality Control

Reproducibility is essential for clinical translation. Critical quality attributes such as particle size, polydispersity index, zeta potential, morphology, drug content, encapsulation efficiency, release profile, sterility, and stability should be appropriately controlled. Standardized analytical methods and validated manufacturing processes are necessary to ensure batch-to-batch consistency and reliable therapeutic performance.

9.5 Regulatory Considerations

Regulatory evaluation of nanomedicines requires detailed information on composition, manufacturing, physicochemical properties, stability, pharmacokinetics, biodistribution, toxicity, and clinical efficacy. Complex systems such as RNA-loaded, biomimetic, multifunctional, and theragnostic nanoparticles may require additional characterization. Harmonized regulatory standards and standardized nanomedicine characterization approaches will facilitate safer and more efficient clinical development.

9.6 Cost, Accessibility, and Commercialization

The commercial success of cancer nanomedicines depends on therapeutic benefit as well as manufacturing cost and accessibility. Complex materials, specialized equipment, and advanced quality-control procedures can increase production costs. Scalable manufacturing and selection of economically feasible materials are therefore important. Future nanomedicines should aim to provide measurable advantages such as improved efficacy, reduced toxicity, enhanced patient convenience, or reduced dosing frequency.

Table 2 Major Challenges in Clinical Translation of Cancer Nanomedicines [33]

Challenge	Key Concern
Safety	Nano toxicity, immune reactions, organ accumulation
Pharmacokinetics (PK)	Variable biodistribution, clearance, and drug release
Manufacturing	Scale-up, process control, and batch consistency





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Reproducibility	Variability in particle size, morphology, drug loading, and stability
Regulation	Complex characterization and evolving regulatory requirements
Cost & Accessibility	High production costs and limited large-scale availability

10. Future Directions and Research Opportunities :

Cancer nanomedicine is rapidly progressing from conventional drug carriers toward intelligent, multifunctional, and biologically responsive delivery systems. Future research is expected to focus on improving tumor selectivity, reducing systemic toxicity, and overcoming biological barriers that limit therapeutic efficacy. Key research opportunities include the development of stimuli-responsive, biomimetic, biodegradable, and multifunctional nanoparticles capable of controlled and site-specific drug release. Integration of nanomedicine with precision oncology, genomics, artificial intelligence, and molecular diagnostics may enable patient-specific selection of Nano therapeutics and optimized treatment strategies.

The delivery of emerging therapeutics such as mRNA, siRNA, CRISPR/Cas systems, proteins, and combination therapies represents another important research direction. Advanced targeting approaches, including tumor microenvironment-responsive and organelle-specific delivery, may further improve intracellular therapeutic activity. Future studies should also emphasize long-term safety, pharmacokinetics, biodistribution, scalable manufacturing, and regulatory standardization. Greater attention to reproducibility and cost-effective production will be necessary to facilitate clinical translation. Overall, future research should move toward simpler, safer, more predictable, and clinically scalable nanocarriers rather than increasing formulation complexity without demonstrable therapeutic benefit.

11. Conclusion

Nanoparticle-mediated drug delivery has emerged as an important approach for improving cancer treatment by enhancing drug delivery, protecting therapeutic molecules, enabling





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controlled release, and facilitating tumor targeting. Recent advances have expanded the field toward smart, stimuli-responsive, biomimetic, multifunctional, and precision nanomedicines. The integration of AI, personalized medicine, gene and RNA delivery, immunotherapy, phototherapy, advanced targeting, and innovative nanomaterials provides significant opportunities for developing next-generation cancer therapeutics. However, challenges related to toxicity, tumor heterogeneity, biodistribution, manufacturing, reproducibility, regulatory approval, and cost continue to limit clinical translation. Future progress will depend on multidisciplinary research that combines nanotechnology with pharmaceutical sciences, molecular biology, computational approaches, and clinical oncology. A balanced focus on therapeutic efficacy, safety, manufacturability, regulatory feasibility, and patient accessibility will be essential for converting promising nanotechnology-based strategies into clinically meaningful cancer treatments.

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