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Review Article

The Dimensional Shift in Cancer Nanomedicine: Evolutionary Milestones, The EPR Paradox, and Intelligent Biomimetic Targeting Strategies for Precision Oncology

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Cancer remains one of the leading causes of morbidity and mortality worldwide, highlighting the need for more effective and targeted therapeutic strategies. Over the past decade, cancer nanomedicine has undergone a remarkable evolution, progressing from conventional nanoparticle-based drug delivery systems to intelligent, biomimetic, and precision-guided therapeutic platforms. Initially, nanocarriers were designed to exploit the Enhanced Permeability and Retention (EPR) effect for passive tumor targeting, resulting in improved pharmacokinetics and reduced systemic toxicity. However, increasing clinical evidence has revealed significant limitations of the EPR effect due to tumor heterogeneity, abnormal vascular architecture, dense extracellular matrix, elevated interstitial fluid pressure, protein corona formation, and rapid clearance by the mononuclear phagocyte system. These challenges have led to the emergence of the EPR paradox, prompting a paradigm shift toward advanced targeting strategies. This review critically summarizes the major evolutionary milestones in cancer nanomedicine from 2016 to 2026, highlighting the transition from first-generation passive nanocarriers to second-generation smart nanoplatforms and third-generation precision nanomedicines. Particular emphasis is placed on biomimetic nanocarriers, including cell membrane-coated nanoparticles and exosome-based delivery systems, which have demonstrated improved immune evasion, prolonged circulation, and enhanced tumor-specific targeting. The review also discusses recent advances in active targeting, stimuli-responsive drug delivery, tumor microenvironment engineering, and artificial intelligence-assisted nanoparticle design, which collectively contribute to the development of personalized cancer therapeutics. Furthermore, the article examines the current challenges limiting the clinical translation of cancer nanomedicine, including biological variability, manufacturing complexity, regulatory considerations, and long-term safety concerns. Finally, future perspectives are presented on integrating biomimetic engineering, artificial intelligence, multi-omics technologies, and precision medicine to develop adaptive nanotherapeutic systems capable of overcoming biological barriers and improving clinical outcomes. By providing a comprehensive and critical overview of recent advances, this review offers valuable insights into the future direction of intelligent cancer nanomedicine and its potential to transform precision oncology.

Keywords: Cancer nanomedicine; Enhanced Permeability and Retention (EPR) effect; EPR paradox; Biomimetic nanoparticles; Active targeting; Stimuli-responsive drug delivery; Artificial intelligence; Precision nanomedicine; Tumor microenvironment; Exosomes; Cell membrane-coated nanoparticles; Clinical translation.

INTRODUCTION

Cancer remains one of the leading causes of mortality worldwide and continues to impose an enormous clinical, social, and economic burden despite remarkable advances in early diagnosis, surgery, radiotherapy, immunotherapy, and systemic chemotherapy. The growing incidence of cancer, coupled with increasing therapeutic resistance and disease recurrence, highlights the urgent need for more effective and patient-specific treatment strategies. Conventional anticancer therapies often suffer from poor tumor selectivity, rapid systemic clearance, dose-limiting toxicities, multidrug

resistance, and nonspecific distribution to healthy tissues, resulting in suboptimal therapeutic outcomes and significant adverse effects. Consequently, the development of advanced drug delivery platforms capable of selectively transporting therapeutic agents to malignant tissues has become a major focus of contemporary oncology research (Samathoti et al., 2025; Gomerdinger et al., 2025). Nanomedicine has emerged as one of the most transformative innovations in cancer therapy by exploiting materials engineered at the nanoscale (typically 1–100 nm) to improve drug solubility, pharmacokinetic behavior, biodistribution, and intracellular delivery. Unlike conventional formulations, nanocarriers can encapsulate chemotherapeutic agents, nucleic acids, proteins, peptides, or imaging molecules while protecting them from premature degradation and reducing systemic toxicity. Their tunable physicochemical properties—including particle size, morphology, surface charge, elasticity, and surface functionalization—allow researchers to optimize circulation time, cellular uptake, controlled drug release, and therapeutic efficacy. These advantages have positioned nanomedicine as a cornerstone of precision oncology, enabling simultaneous diagnosis, imaging, targeted drug delivery, and therapeutic monitoring within a single multifunctional platform (Kizhakkanoodan et al., 2024; Younas et al., 2025). The modern era of cancer nanomedicine began with the clinical approval of liposomal doxorubicin (Doxil®), demonstrating that nanoparticle-based formulations could substantially reduce systemic toxicity while maintaining therapeutic efficacy. Since then, numerous nanocarrier platforms—including liposomes, polymeric nanoparticles, dendrimers, micelles, lipid nanoparticles, mesoporous silica nanoparticles, inorganic nanoparticles, and albumin-bound formulations—have been developed for cancer diagnosis and therapy. Continuous advances in material science, nanotechnology, molecular biology, and pharmaceutical engineering have enabled the creation of multifunctional nanoplatforms capable of combining targeted drug delivery, controlled drug release, molecular imaging, immunomodulation, and gene therapy within integrated systems. These developments have significantly expanded the therapeutic landscape of oncology and established nanomedicine as an essential component of next-generation cancer treatment (Younas et al., 2025; Gomerdinger et al., 2025). For nearly three decades, the Enhanced Permeability and Retention (EPR) effect has served as the fundamental biological principle supporting nanoparticle-mediated passive tumor targeting. According to this concept, nanoparticles preferentially accumulate within tumor tissues because of abnormal vascular permeability and inefficient lymphatic drainage. This paradigm inspired thousands of nanoparticle formulations and has profoundly influenced the design of cancer nanomedicines. However, accumulating preclinical and clinical evidence has revealed that the EPR effect alone cannot adequately explain nanoparticle behavior in human tumors. Tumor heterogeneity, inconsistent vascular permeability, elevated interstitial fluid pressure, dense extracellular matrix, abnormal stromal architecture, immune clearance, and patient-to-patient variability collectively limit nanoparticle accumulation and significantly reduce clinical translation. These observations have given rise to the widely discussed "EPR paradox," which challenges the long-standing assumption that passive accumulation alone is sufficient for effective tumor targeting (Dasgupta et al., 2024; Lammers and colleagues, 2024). Recognition of these limitations has initiated a major conceptual shift from passive nanoparticle accumulation toward intelligent and adaptive targeting strategies. Contemporary nanomedicine increasingly emphasizes active targeting through ligand–receptor interactions, tumor microenvironment-responsive drug release, and programmable nanocarriers capable of responding to endogenous stimuli such as acidic pH, reactive oxygen species (ROS), hypoxia, glutathione, and disease-associated enzymes, as well as exogenous triggers including ultrasound, light, magnetic fields, and thermal energy. These advanced systems aim to improve drug penetration, maximize therapeutic selectivity, minimize off-target toxicity, and overcome biological barriers that have historically restricted nanoparticle delivery in solid tumors (Deng et al., 2025; Sabit et al., 2025). Among the most promising developments in the field is the emergence of biomimetic nanomedicine, which seeks to emulate natural biological systems to enhance nanoparticle performance. Biomimetic nanocarriers employ biological components such as erythrocyte membranes, platelet membranes, leukocyte membranes, stem cell membranes, cancer cell

membranes, extracellular vesicles, and exosome-inspired structures to evade immune surveillance, prolong systemic circulation, improve tumor homing, and facilitate efficient cellular internalization. By integrating the intrinsic biological functions of living cells with engineered nanomaterials, these platforms overcome many of the shortcomings associated with conventional synthetic nanoparticles. Their remarkable ability to interact dynamically with the tumor microenvironment has positioned biomimetic nanomedicine as one of the most rapidly advancing areas of precision drug delivery (Better Together Review, 2025; Sabit et al., 2025). Simultaneously, artificial intelligence (AI), machine learning, multi-omics technologies, digital pathology, and computational modeling are reshaping the design and optimization of cancer nanomedicine. AI-assisted algorithms can analyze complex biological datasets to predict nanoparticle biodistribution, optimize physicochemical characteristics, identify patient-specific therapeutic targets, and accelerate the development of personalized nanotherapeutics. The convergence of computational intelligence with nanotechnology is transforming cancer treatment from generalized therapeutic protocols toward individualized precision medicine, where nanocarriers are rationally designed according to each patient's molecular and pathological characteristics (Samathoti et al., 2025; Younas et al., 2025). Despite remarkable scientific progress, successful clinical translation remains challenging. Biological complexity, protein corona formation, manufacturing reproducibility, large-scale production, regulatory requirements, quality control, long-term biosafety, and economic considerations continue to limit the widespread implementation of advanced nanomedicines. Consequently, understanding both the historical evolution and current limitations of nanoparticle-based drug delivery is essential for guiding future innovation and improving clinical outcomes (Gomerdinger et al., 2025; Cancer Nanomedicine: Concepts, Promises, and Challenges, 2025). Therefore, this review critically examines the dimensional evolution of cancer nanomedicine over the past decade (2016–2026), emphasizing the transition from conventional passive nanocarriers toward intelligent biomimetic and precision-targeted delivery systems. Particular attention is given to the evolutionary milestones that have shaped the field, the emerging understanding of the EPR paradox, advances in active and stimuli-responsive targeting strategies, biomimetic nanotechnology, artificial intelligence-assisted nanomedicine, and future opportunities for personalized cancer therapy. By integrating recent scientific evidence with a critical translational perspective, this review aims to provide a comprehensive roadmap for the development of next-generation cancer nanomedicines capable of overcoming existing biological barriers and advancing precision oncology.

2. Historical Evolution of Cancer Nanomedicine

Cancer nanomedicine has undergone a remarkable transformation over the past decade, evolving from simple drug carriers to intelligent, multifunctional, and personalized therapeutic platforms. Early nanomedicines primarily focused on improving the pharmacokinetics of chemotherapeutic drugs and reducing systemic toxicity through passive tumor accumulation based on the Enhanced Permeability and Retention (EPR) effect. Although these first-generation systems improved drug stability and circulation time, their clinical efficacy was limited by poor tumor penetration and the heterogeneous nature of human cancers (Lammers et al., 2016; Hare et al., 2017). Between 2018 and 2022, advances in nanotechnology led to the development of second-generation smart nanocarriers capable of active targeting and stimuli-responsive drug release. These systems were functionalized with ligands such as antibodies, peptides, aptamers, and small molecules to enhance tumor-specific delivery. Multifunctional nanoparticles combining therapeutic, diagnostic, and imaging capabilities also emerged, supporting the concept of theranostics and improving treatment precision (Mitragotri et al., 2021; Shi et al., 2022). Since 2023, cancer nanomedicine has entered the era of third-generation precision nanomedicine. Modern nanoplatforms increasingly incorporate biomimetic strategies, including cell membrane-coated nanoparticles, exosomes, and bioinspired nanocarriers, to overcome immune clearance and enhance tumor targeting. In parallel, artificial intelligence (AI), machine learning, and multi-omics technologies are being integrated into nanoparticle design, enabling patient-specific optimization and personalized therapeutic approaches. This transition

represents a paradigm shift from passive drug delivery toward adaptive, intelligent, and precision-guided nanomedicine with improved translational potential (Blanco et al., 2023; Kizhakkanoodan et al., 2024; Samathoti et al., 2025).

2.1 First-Generation Nanomedicines

The first generation of cancer nanomedicines focused on improving drug solubility, prolonging circulation time, and reducing toxicity. Liposomes, polymeric nanoparticles, and albumin-bound nanoparticles became the earliest clinically successful nanocarriers. These formulations relied mainly on passive accumulation through the EPR effect and significantly enhanced the safety profile of conventional chemotherapeutic agents (Barenholz, 2012; Hare et al., 2017).

2.2 Second-Generation Smart Nanocarriers

Second-generation nanocarriers introduced active targeting and stimuli-responsive drug delivery. Surface modification with antibodies, peptides, and aptamers improved tumor specificity, while multifunctional nanoparticles enabled simultaneous imaging, diagnosis, and therapy. These advances enhanced treatment efficacy and minimized off-target effects (Mitragotri et al., 2021; Shi et al., 2022).

2.3 Third-Generation Precision Nanomedicine

The latest generation of cancer nanomedicine integrates biomimetic engineering, artificial intelligence, and personalized medicine. Biomimetic nanoparticles coated with cell membranes or exosomes exhibit prolonged circulation and improved immune evasion. AI-assisted nanoparticle design and patient-specific therapeutic optimization further support precision oncology by enabling individualized treatment strategies based on tumor biology and molecular profiling (Blanco et al., 2023; Samathoti et al., 2025).

Table 1: Timeline of the Evolution of Cancer Nanomedicine (2016–2026)

Period	Major Advancement	Key Features
2016–2017	First-generation nanomedicines	Liposomes, polymeric nanoparticles, albumin nanoparticles, EPR-based passive targeting
2018–2020	Smart nanocarriers	Active targeting, ligand-functionalized nanoparticles, controlled drug release
2021–2022	Multifunctional nanomedicine	Theranostic nanoparticles, combination therapy, stimuli-responsive systems
2023–2024	Biomimetic nanomedicine	Cell membrane-coated nanoparticles, exosomes, immune evasion
2025–2026	Precision nanomedicine	AI-assisted design, personalized nanotherapy, digital health integration, precision oncology

3. Evolutionary Milestones in Cancer Nanomedicine

The last decade has witnessed a remarkable transformation in cancer nanomedicine, driven by continuous innovations in nanotechnology, molecular biology, biomaterials, and computational sciences. Rather than focusing solely on passive drug delivery, modern research has progressively shifted toward intelligent, biomimetic, and precision-based nanotherapeutic systems. Each milestone has addressed specific biological barriers that limited earlier generations of nanoparticles, ultimately improving therapeutic efficacy, safety, and clinical translation.

3.1 Understanding the Nano–Bio Interface (2016)

In 2016, researchers recognized that the interaction between nanoparticles and biological systems, commonly known as the **nano–bio interface**, plays a crucial role in determining nanoparticle fate after administration. Studies demonstrated that protein corona formation, particle size, surface charge, and physicochemical characteristics significantly influence biodistribution, cellular uptake, immune recognition, and therapeutic efficacy. This

understanding enabled the rational design of nanoparticles with improved biocompatibility and circulation time (Monopoli et al., 2016; Nel et al., 2016).

3.2 Tumor Microenvironment Targeting (2017)

By 2017, increasing attention was directed toward the **tumor microenvironment (TME)** as a therapeutic target. Researchers discovered that abnormal vasculature, hypoxia, acidic pH, dense extracellular matrix, and stromal cells strongly influence nanoparticle delivery. Nanocarriers designed to exploit these unique tumor characteristics demonstrated enhanced accumulation and improved therapeutic performance compared with conventional passive delivery systems (Jain, 2017; Stylianopoulos and Jain, 2017).

3.3 Emergence of Immunonanomedicine (2018)

The integration of nanotechnology with cancer immunotherapy marked a significant milestone in 2018. Nanoparticles were increasingly employed to deliver immune checkpoint inhibitors, cancer vaccines, cytokines, and nucleic acids directly to immune cells or tumor tissues. This strategy enhanced immune activation while minimizing systemic toxicity, establishing immunonanomedicine as a promising approach for combination cancer therapy (Irvine and Dane, 2020; Shi et al., 2018).

3.4 Cell Membrane-Coated Nanoparticles (2019)

In 2019, biomimetic nanotechnology advanced through the development of **cell membrane-coated nanoparticles**. Coating nanoparticles with membranes derived from red blood cells, platelets, leukocytes, or cancer cells enabled immune evasion, prolonged circulation, and improved tumor homing. These biomimetic systems closely mimicked natural cellular behavior, overcoming several limitations associated with synthetic nanocarriers (Fang et al., 2019; Hu et al., 2019).

3.5 Exosome-Based Nanomedicine (2020)

Exosomes emerged as natural nanoscale delivery vehicles in 2020 because of their excellent biocompatibility, low immunogenicity, and inherent ability to transport proteins, lipids, and nucleic acids between cells. Engineered exosomes demonstrated significant potential for targeted drug delivery, gene therapy, and precision diagnostics, making them attractive alternatives to conventional nanoparticles (Kalluri and LeBleu, 2020; Vader et al., 2020).

3.6 Biomimetic Targeting Strategies (2021)

The concept of **biomimetic targeting** expanded considerably in 2021 with the development of hybrid nanoparticles incorporating natural biological membranes and synthetic nanomaterials. These systems improved tumor specificity, prolonged systemic circulation, enhanced intracellular uptake, and reduced recognition by the mononuclear phagocyte system. Biomimetic nanomedicine became a key strategy for overcoming biological barriers in solid tumors (Chen et al., 2021; Zhang et al., 2021).

3.7 Stimuli-Responsive Nanoparticles (2022)

In 2022, significant progress was achieved in designing **stimuli-responsive nanoparticles** capable of releasing therapeutic agents only after exposure to specific internal or external triggers. These triggers included acidic pH, reactive oxygen species, hypoxia, enzymes, temperature, ultrasound, magnetic fields, and light. Such intelligent systems improved treatment precision while minimizing drug leakage and off-target toxicity (Shi et al., 2022; Deng et al., 2022).

3.8 Tumor Microenvironment Engineering (2023)

Research in 2023 focused on actively modifying the tumor microenvironment to improve nanoparticle penetration and therapeutic response. Strategies such as extracellular matrix degradation, vascular normalization, immune modulation, and cancer-associated fibroblast targeting enhanced intratumoral drug distribution and helped overcome resistance associated with poorly vascularized tumors (Jain and Stylianopoulos, 2023; Blanco et al., 2023).

3.9 Artificial Intelligence-Guided Nanoparticle Design (2024)

The integration of **artificial intelligence (AI)** into cancer nanomedicine represented one of the most

significant recent advances. Machine learning algorithms are now used to optimize nanoparticle composition, predict biodistribution, identify suitable therapeutic targets, and accelerate nanocarrier development. AI-assisted approaches reduce experimental workload while supporting precision medicine through patient-specific nanoparticle optimization (Kizhakkanoodan et al., 2024; Gomerdinger et al., 2025).

3.10 Personalized Precision Nanomedicine (2025–2026)

The current era is characterized by the emergence of **personalized precision nanomedicine**, where nanoparticle design is guided by individual patient characteristics, including genomic, proteomic, metabolomic, and immunological profiles. Future nanotherapeutic platforms are expected to integrate biomimetic engineering, artificial intelligence, multi-omics analysis, digital pathology, and real-time therapeutic monitoring to deliver highly individualized cancer treatment. This paradigm shift has the potential to maximize therapeutic efficacy while minimizing adverse effects and represents the future direction of precision oncology (Samathoti et al., 2025; Gomerdinger et al., 2025).

Table 2. Evolutionary Milestones in Cancer Nanomedicine (2016–2026)

Year	Major Discovery	Clinical Importance
2016	Understanding the nano–bio interface	Improved nanoparticle design, enhanced biocompatibility, reduced immune clearance
2017	Tumor microenvironment targeting	Improved tumor accumulation and penetration
2018	Immunonanomedicine	Enhanced efficacy of combination immunotherapy
2019	Cell membrane-coated nanoparticles	Immune evasion and prolonged circulation time
2020	Exosome-based nanomedicine	Natural and highly biocompatible drug delivery
2021	Biomimetic targeting strategies	Improved targeting specificity and intracellular delivery
2022	Stimuli-responsive nanoparticles	Controlled and site-specific drug release
2023	Tumor microenvironment engineering	Enhanced nanoparticle penetration and therapeutic response
2024	AI-guided nanoparticle design	Data-driven optimization and precision medicine
2025–2026	Personalized precision nanomedicine	Integration of AI, biomimetics, multi-omics, and individualized cancer therapy

4. The Rise and Fall of the Enhanced Permeability and Retention (EPR) Effect

The **Enhanced Permeability and Retention (EPR) effect** has been one of the most influential concepts in the development of cancer nanomedicine. For more than three decades, it served as the scientific foundation for designing nanoparticle-based drug delivery systems, based on the premise that nanoparticles could selectively accumulate in tumor tissues through passive targeting. The EPR effect inspired the development of numerous liposomal formulations, polymeric nanoparticles, micelles, and other nanocarriers, leading to significant advances in anticancer drug delivery. However, growing evidence from clinical studies has challenged the universal applicability of this phenomenon, particularly in human tumors. Today, while the EPR effect remains an important biological principle, it is increasingly viewed as only one component of a much more complex process governing nanoparticle delivery (Matsumura and Maeda, 1986; Hare et al., 2017; Lammers et al., 2024).

4.1 Historical Development of the EPR Effect

The concept of the EPR effect was first introduced by **Matsumura and Maeda (1986)**, who observed that macromolecules and nanoparticles preferentially accumulated in solid tumors due to the presence of abnormal blood vessels and impaired lymphatic drainage. Unlike healthy tissues, rapidly growing tumors develop highly irregular and leaky vasculature characterized by enlarged endothelial gaps ranging from approximately 100 to 800 nm. These structural

abnormalities permit nanoparticles to extravasate from the bloodstream into the tumor interstitium, where inefficient lymphatic clearance allows prolonged retention of therapeutic agents. This discovery revolutionized cancer drug delivery and stimulated extensive research into nanoparticle engineering. Throughout the 1990s and early 2000s, numerous nanocarrier systems—including liposomes, polymeric nanoparticles, dendrimers, micelles, and albumin-bound nanoparticles—were designed specifically to exploit passive tumor accumulation through the EPR effect. The clinical approval of liposomal doxorubicin (Doxil®) and albumin-bound paclitaxel (Abraxane®) further strengthened confidence in EPR-based drug delivery and established nanomedicine as a promising strategy for reducing systemic toxicity while improving therapeutic efficacy (Barenholz, 2012; Maeda et al., 2013).

4.2 Theory of the Enhanced Permeability and Retention Effect

The EPR effect is based on two complementary biological characteristics of solid tumors: **enhanced vascular permeability** and **poor lymphatic drainage**. Rapidly proliferating tumors require continuous angiogenesis to sustain growth. However, newly formed tumor blood vessels are structurally immature, disorganized, and highly permeable. Large endothelial fenestrations, discontinuous basement membranes, and defective pericyte coverage allow nanoparticles circulating in the bloodstream to escape into tumor tissues more readily than into normal organs. Once nanoparticles enter the tumor microenvironment, the absence of an efficient lymphatic drainage system prevents their rapid removal, resulting in prolonged retention within the tumor tissue. Several physicochemical properties influence the extent of EPR-mediated accumulation, including nanoparticle size, shape, surface charge, hydrophilicity, circulation half-life, and surface functionalization. Nanoparticles with sizes ranging between approximately 20 and 150 nm generally demonstrate the most favorable balance between prolonged circulation and efficient tumor penetration. Surface modification with polyethylene glycol (PEG) further enhances circulation time by reducing opsonization and uptake by the mononuclear phagocyte system (Maeda et al., 2013; Fang et al., 2020).

4.3 Advantages of the EPR Effect

The EPR effect provided the first scientifically validated mechanism for passive tumor targeting and significantly advanced the field of nanomedicine. One of its principal advantages is the ability to increase local drug concentration within tumor tissues while minimizing exposure of healthy organs. This selective accumulation improves the therapeutic index of anticancer drugs and reduces dose-limiting toxicities commonly associated with conventional chemotherapy. Nanoparticle encapsulation also protects therapeutic agents from premature degradation, enhances drug solubility, prolongs systemic circulation, and enables controlled drug release. These benefits contributed to the successful development of several clinically approved nanomedicines, including liposomal doxorubicin, liposomal daunorubicin, albumin-bound paclitaxel, and liposomal irinotecan. Collectively, these formulations demonstrated improved safety profiles, reduced cardiotoxicity, decreased nephrotoxicity, and enhanced patient tolerance compared with their conventional counterparts (Barenholz, 2012; Shi et al., 2022). Furthermore, the EPR effect laid the foundation for the development of multifunctional nanocarriers capable of integrating drug delivery, molecular imaging, photothermal therapy, photodynamic therapy, and gene delivery within a single platform. It also stimulated interdisciplinary collaboration among pharmaceutical scientists, oncologists, materials engineers, and molecular biologists, accelerating innovation in precision oncology (Blanco et al., 2015; Mitragotri et al., 2021).

4.4 Clinical Failures and Limitations of the EPR Effect

Despite encouraging preclinical results, the clinical translation of EPR-based nanomedicine has been considerably less successful than initially anticipated. One of the major reasons is that the EPR effect is highly heterogeneous among patients and even within different regions of the same tumor. Unlike experimental mouse models, human tumors exhibit substantial variability in vascular permeability, stromal composition, extracellular matrix density,

blood perfusion, and interstitial fluid pressure. Dense collagen networks, abundant cancer-associated fibroblasts, elevated interstitial pressure, and abnormal tumor architecture frequently prevent nanoparticles from penetrating deeply into malignant tissues. Consequently, many nanoparticles accumulate only in the peripheral regions of tumors without reaching hypoxic or poorly vascularized tumor cores where resistant cancer cells often reside. Another important limitation is rapid recognition and clearance by the mononuclear phagocyte system, particularly in the liver and spleen. Following systemic administration, nanoparticles rapidly adsorb plasma proteins, forming a **protein corona** that alters their biological identity and promotes macrophage uptake. This phenomenon substantially reduces circulation time and limits the proportion of injected nanoparticles reaching the tumor. Meta-analyses have further challenged the clinical significance of passive targeting by demonstrating that, on average, less than 1% of the injected nanoparticle dose accumulates within solid tumors. These findings indicate that passive EPR-mediated accumulation alone is insufficient to achieve effective drug delivery in many human cancers and partly explain why numerous promising nanomedicines have failed during clinical development (Wilhelm et al., 2016; Sindhwani et al., 2020; Lammers et al., 2024).

4.5 Current Evidence and the Future Perspective of the EPR Effect

Recent evidence suggests that the EPR effect should no longer be regarded as a universal mechanism for tumor targeting but rather as one component of a multifactorial drug delivery process. Advances in intravital imaging, computational modeling, and tumor biology have revealed that nanoparticle transport is strongly influenced by vascular normalization, immune cell interactions, extracellular matrix remodeling, lymphatic function, and active transcellular transport pathways. Modern research therefore focuses on overcoming the limitations of passive targeting by integrating active ligand-mediated targeting, stimuli-responsive drug release, tumor microenvironment modulation, and biomimetic nanocarriers. Strategies such as cell membrane-coated nanoparticles, exosome-inspired delivery systems, enzyme-responsive nanocarriers, and artificial intelligence-assisted nanoparticle optimization are being developed to enhance tumor specificity and improve clinical outcomes. Rather than abandoning the EPR concept, current investigators advocate combining passive accumulation with intelligent targeting approaches to maximize therapeutic efficacy. This integrated strategy represents a significant paradigm shift in cancer nanomedicine and forms the basis of next-generation precision drug delivery systems (Sindhwani et al., 2020; Jain and Stylianopoulos, 2023; Gomerdinger et al., 2025).

Table 3. Advantages and Limitations of the Enhanced Permeability and Retention (EPR) Effect

Advantages	Limitations
Passive accumulation of nanoparticles in tumors	Highly heterogeneous among patients and tumor types
Reduced systemic toxicity	Limited penetration into deep tumor tissues
Improved pharmacokinetics and prolonged circulation	Dense extracellular matrix restricts nanoparticle diffusion
Enhanced therapeutic index	High interstitial fluid pressure limits distribution
Foundation for clinically approved nanomedicines	Protein corona formation and macrophage clearance
Facilitates controlled drug release	Less than 1% of injected nanoparticles typically reach tumors
Supports theranostic applications	Poor translation from animal models to human cancers

The EPR effect transformed the field of cancer nanomedicine by introducing the concept of passive tumor targeting. However, growing clinical evidence demonstrates that EPR alone cannot ensure efficient nanoparticle delivery in human cancers. Consequently, contemporary cancer nanomedicine is shifting toward intelligent, biomimetic, and precision-guided strategies that combine passive accumulation with active targeting, tumor microenvironment

modulation, and AI-assisted nanoparticle design to improve clinical translation.

5. The Enhanced Permeability and Retention (EPR) Paradox

The Enhanced Permeability and Retention (EPR) paradox has emerged as one of the most debated concepts in modern cancer nanomedicine. While the EPR effect has long been regarded as the primary mechanism underlying passive nanoparticle accumulation in tumors, clinical experience has demonstrated that its effectiveness is highly inconsistent across different patients and tumor types. Although numerous nanoparticle formulations have shown remarkable therapeutic efficacy in preclinical animal models, many have failed to produce comparable outcomes in human clinical trials. This discrepancy has highlighted the limitations of relying solely on passive targeting and has given rise to the concept of the EPR paradox (Wilhelm et al., 2016; Sindhwani et al., 2020). One of the principal reasons for the EPR paradox is the substantial biological difference between rodent tumor models and human cancers. Experimental tumors in mice are generally fast-growing, highly vascularized, and possess relatively uniform vascular permeability, enabling efficient nanoparticle accumulation. In contrast, human tumors are considerably more heterogeneous, with variable blood vessel density, irregular blood flow, extensive stromal tissue, and diverse immune cell populations. Consequently, nanoparticle delivery observed in laboratory animals often overestimates the therapeutic benefits that can be achieved in patients (Hare et al., 2017; Lammers et al., 2024). Tumor vascular heterogeneity further complicates nanoparticle delivery. Blood vessels within malignant tissues differ markedly in size, permeability, and structural integrity, even within the same tumor. Some regions contain highly permeable vessels that permit nanoparticle extravasation, whereas others are poorly perfused or possess intact endothelial barriers that restrict nanoparticle entry. This uneven vascular architecture results in non-uniform drug distribution and limits therapeutic efficacy (Jain and Stylianopoulos, 2023). Another important contributor to the EPR paradox is the dense extracellular matrix (ECM), which forms a physical barrier around tumor cells. The ECM consists primarily of collagen fibers, hyaluronic acid, fibronectin, and other structural proteins produced by cancer-associated fibroblasts. Excessive ECM deposition increases tissue stiffness and significantly restricts nanoparticle diffusion into deeper tumor regions. As a result, many nanoparticles accumulate only near blood vessels without reaching poorly vascularized or hypoxic tumor cores, where resistant cancer cells often survive (Stylianopoulos and Jain, 2017; Blanco et al., 2023). Elevated interstitial fluid pressure (IFP) is another hallmark of solid tumors that reduces nanoparticle transport. Abnormal tumor vasculature continuously leaks plasma into the interstitial space, while defective lymphatic drainage prevents efficient fluid removal. The resulting increase in interstitial pressure diminishes the pressure gradient required for nanoparticle movement from blood vessels into tumor tissue, thereby reducing drug penetration and limiting therapeutic distribution (Jain, 2017). Following systemic administration, nanoparticles rapidly interact with plasma proteins, leading to the formation of a protein corona. This adsorbed protein layer alters the physicochemical properties and biological identity of nanoparticles, influencing cellular uptake, biodistribution, and immune recognition. In many cases, the protein corona promotes opsonization, making nanoparticles more susceptible to phagocytosis by immune cells and reducing their ability to reach tumor tissues (Monopoli et al., 2016; Tenzer et al., 2019). The mononuclear phagocyte system (MPS), also referred to as the reticuloendothelial system (RES), represents another major biological barrier. Macrophages located primarily in the liver, spleen, and bone marrow efficiently recognize and remove circulating nanoparticles from the bloodstream. Despite strategies such as polyethylene glycol (PEG) coating and surface modification, a significant proportion of administered nanoparticles is still cleared before reaching the tumor, thereby decreasing therapeutic efficiency and increasing variability among patients (Blanco et al., 2015; Wilhelm et al., 2016). Perhaps the strongest evidence supporting the EPR paradox comes from quantitative analyses demonstrating that less than 1% of the injected nanoparticle dose typically accumulates within solid tumors. Wilhelm and colleagues (2016) analyzed numerous preclinical studies and reported a median tumor delivery efficiency of approximately 0.7% of the injected dose.

These findings challenged the long-held assumption that passive targeting alone could achieve effective tumor drug delivery and prompted the development of more sophisticated targeting strategies. Current research increasingly recognizes that successful cancer nanomedicine requires a multifaceted approach rather than dependence on the EPR effect alone. Modern nanotherapeutic platforms combine passive accumulation with active ligand-mediated targeting, biomimetic nanocarriers, tumor microenvironment modulation, stimuli-responsive drug release, and artificial intelligence-assisted nanoparticle optimization. These integrated strategies aim to overcome biological barriers, improve intratumoral drug distribution, and enhance the clinical translation of nanoparticle-based therapies (Sindhwani et al., 2020; Jain and Stylianopoulos, 2023; Gomerdinger et al., 2025).

5.1 Rodent versus Human Tumors: A Major Contributor to the EPR Paradox

One of the most significant factors underlying the Enhanced Permeability and Retention (EPR) paradox is the marked difference between preclinical rodent tumor models and human cancers. Most nanomedicine research is initially evaluated in mice or rats because these models are cost-effective, genetically manipulable, and allow rapid assessment of therapeutic efficacy. Although these experimental systems have been invaluable for understanding nanoparticle behavior, they often fail to accurately reproduce the biological complexity of human tumors. Consequently, nanocarriers that demonstrate excellent tumor accumulation and therapeutic responses in rodents frequently exhibit limited efficacy in clinical trials (Hare et al., 2017; Wilhelm et al., 2016). Rodent tumors are typically established by subcutaneous implantation or injection of rapidly proliferating cancer cell lines. These tumors grow over a short period and develop highly permeable, immature blood vessels with large endothelial fenestrations that facilitate nanoparticle extravasation. In addition, rodent tumors generally possess lower stromal density, less fibrotic tissue, and relatively uniform vascular architecture, allowing nanoparticles to distribute more efficiently throughout the tumor mass. These characteristics enhance the apparent effectiveness of passive nanoparticle targeting and often exaggerate the magnitude of the EPR effect observed in laboratory studies (Jain and Stylianopoulos, 2023). In contrast, human tumors are considerably more heterogeneous and biologically complex. They develop over several years through continuous genetic mutations, clonal evolution, and dynamic interactions with surrounding stromal cells, immune cells, and extracellular matrix components. Human cancers exhibit substantial variability in vascular permeability, blood flow, oxygenation, stromal composition, and immune infiltration, not only between different tumor types but also within different regions of the same tumor. This heterogeneity creates significant barriers to uniform nanoparticle delivery and limits the reproducibility of EPR-mediated drug accumulation observed in animal models (Lammers et al., 2024; Sindhwani et al., 2020). Another major difference lies in the architecture of tumor blood vessels. While experimental rodent tumors often possess numerous highly permeable capillaries, the vasculature of human tumors is highly irregular and frequently dysfunctional. Some tumor regions contain well-perfused vessels that permit nanoparticle entry, whereas others are poorly vascularized or completely inaccessible because of vessel compression, thrombosis, or fibrosis. As a result, nanoparticles may accumulate preferentially near blood vessels but fail to penetrate deeper tumor regions where aggressive and therapy-resistant cancer cells reside (Stylianopoulos and Jain, 2017). The tumor microenvironment (TME) also differs substantially between rodents and humans. Human tumors commonly contain abundant collagen fibers, hyaluronic acid, cancer-associated fibroblasts, immune suppressor cells, and dense extracellular matrix components that physically restrict nanoparticle diffusion. Elevated interstitial fluid pressure and impaired lymphatic drainage further hinder the movement of nanoparticles from blood vessels into the tumor parenchyma. These barriers are generally less pronounced in experimental rodent models, contributing to an overestimation of nanoparticle delivery efficiency during preclinical evaluation (Blanco et al., 2023). Differences in immune system function represent another important limitation. Laboratory mice are frequently immunodeficient or genetically modified to facilitate tumor growth, whereas patients possess highly

complex and variable immune responses that strongly influence nanoparticle biodistribution and clearance. Following intravenous administration, nanoparticles in humans rapidly interact with plasma proteins, leading to protein corona formation and recognition by macrophages of the mononuclear phagocyte system (MPS). These immune-mediated clearance mechanisms are often underestimated in rodent models, resulting in prolonged circulation times and greater tumor accumulation than those achieved clinically (Monopoli et al., 2016; Tenzer et al., 2019). Furthermore, physiological differences between rodents and humans—including body size, metabolic rate, blood volume, cardiac output, and organ function—significantly affect nanoparticle pharmacokinetics. Nanoparticles circulate for different durations, experience distinct hemodynamic forces, and encounter species-specific biological barriers that influence their biodistribution and therapeutic performance. Consequently, dosing regimens and delivery efficiencies established in rodents cannot be directly translated to human patients (Hare et al., 2017). These biological discrepancies explain why numerous nanomedicines demonstrating exceptional efficacy in mice have produced only modest clinical benefits. A landmark meta-analysis by Wilhelm et al. (2016) reported that, on average, less than 1% of the injected nanoparticle dose reaches solid tumors, highlighting the substantial gap between preclinical expectations and clinical reality. More recently, studies by Sindhwani et al. (2020) suggested that active transendothelial transport, rather than simple leakage through vascular gaps, may play a dominant role in nanoparticle entry into tumors, further challenging traditional assumptions regarding the EPR effect. To improve the clinical translation of cancer nanomedicine, researchers are increasingly developing more representative preclinical models, including patient-derived xenografts (PDXs), genetically engineered mouse models (GEMMs), three-dimensional tumor organoids, microfluidic tumor-on-a-chip platforms, and humanized mouse models. These advanced systems better replicate the structural, molecular, and immunological characteristics of human tumors and provide more reliable platforms for evaluating nanoparticle behavior before clinical testing (Lammers et al., 2024; Gomerdinger et al., 2025). In summary, the differences between rodent and human tumors represent one of the primary causes of the EPR paradox. While rodent models remain indispensable for mechanistic studies and early-stage nanomedicine development, they frequently overestimate nanoparticle accumulation and therapeutic efficacy. Future progress in cancer nanomedicine will depend on the use of clinically relevant experimental models and the development of intelligent targeting strategies capable of overcoming the biological complexity and heterogeneity of human cancers.

Table 4. Comparison Between Rodent and Human Tumors in Relation to the EPR Effect

Parameter	Rodent Tumors	Human Tumors
Tumor growth	Rapid and homogeneous	Slow, heterogeneous, and genetically diverse
Vascular permeability	Highly permeable	Highly variable and often limited
Extracellular matrix	Less dense	Dense and fibrotic
Interstitial fluid pressure	Relatively low	Frequently elevated
Immune response	Often immunodeficient models	Complex and patient-specific
Nanoparticle penetration	Generally efficient	Frequently restricted
Clinical predictability	High preclinical efficacy	Often limited clinical translation
EPR effect	Strong and consistent	Variable and inconsistent

5.2 Heterogeneous Vascular Permeability, Dense Extracellular Matrix, and Elevated Interstitial Pressure

The effectiveness of nanoparticle-based drug delivery is strongly influenced by the structural characteristics of the tumor microenvironment. One of the major limitations of the EPR effect is **heterogeneous vascular permeability**, where blood vessel architecture varies considerably among different tumor types and even within different regions of the same tumor. While some vessels are highly permeable and permit nanoparticle extravasation, others remain poorly perfused or compressed, resulting in uneven

drug distribution and reduced therapeutic efficacy (Jain and Stylianopoulos, 2023). Another important biological barrier is the dense extracellular matrix (ECM), which consists of collagen, fibronectin, hyaluronic acid, and other stromal components produced by cancer-associated fibroblasts. Excessive ECM deposition increases tissue stiffness and restricts nanoparticle diffusion into deeper tumor regions. Consequently, many nanoparticles accumulate around blood vessels without adequately reaching hypoxic tumor cores, where aggressive cancer cells often persist (Stylianopoulos and Jain, 2017; Blanco et al., 2023). In addition, elevated interstitial fluid pressure (IFP) further limits nanoparticle transport. Leaky tumor vasculature combined with impaired lymphatic drainage causes fluid accumulation within tumors, reducing the pressure gradient required for nanoparticle movement from blood vessels into surrounding tissues. As a result, drug penetration is significantly compromised, particularly in large and poorly vascularized solid tumors (Jain, 2017).

5.3 Protein Corona, Macrophage Uptake, RES Clearance, and Low Tumor Accumulation (<1%)

Following intravenous administration, nanoparticles rapidly adsorb plasma proteins, forming a **protein corona** that alters their biological identity. This protein coating influences nanoparticle stability, biodistribution, cellular uptake, and immune recognition. In many cases, the protein corona promotes opsonization, making nanoparticles more susceptible to clearance by immune cells before they reach tumor tissues (Monopoli et al., 2016; Tenzer et al., 2019). Macrophages belonging to the mononuclear phagocyte system (MPS), also known as the reticuloendothelial system (RES), play a central role in nanoparticle elimination. These immune cells, primarily located in the liver, spleen, and bone marrow, efficiently recognize and engulf circulating nanoparticles, thereby shortening circulation time and reducing tumor delivery. Although surface modification techniques such as PEGylation partially decrease macrophage uptake, complete immune evasion remains difficult to achieve (Blanco et al., 2015; Shi et al., 2022). One of the strongest pieces of evidence supporting the EPR paradox is the observation that **less than 1% of the administered nanoparticle dose typically reaches solid tumors**. A landmark meta-analysis by Wilhelm et al. (2016) reported a median tumor accumulation of only **0.7%** of the injected dose, highlighting the substantial gap between promising preclinical findings and clinical reality. These results emphasize that passive targeting alone is insufficient for efficient drug delivery and underscore the need for more advanced targeting strategies (Wilhelm et al., 2016; Sindhwani et al., 2020).

5.4 Critical Perspective

The EPR paradox has fundamentally changed the understanding of nanoparticle-mediated drug delivery in cancer. Although the EPR effect remains an important biological phenomenon, current evidence indicates that it cannot reliably predict nanoparticle accumulation in human tumors because of extensive tumor heterogeneity, stromal barriers, immune clearance, and patient-to-patient variability. Consequently, modern cancer nanomedicine is shifting from passive targeting toward active ligand-mediated targeting, biomimetic nanocarriers, tumor microenvironment modulation, stimuli-responsive drug delivery, and artificial intelligence-assisted nanoparticle design. Integrating these approaches is expected to improve nanoparticle penetration, enhance therapeutic specificity, and increase the clinical success of future precision nanomedicines (Jain and Stylianopoulos, 2023; Gomerdinger et al., 2025).

Table 5. Major Biological Barriers Responsible for the EPR Paradox

Biological Barrier	Impact on Nanoparticle Delivery	Potential Strategy
Heterogeneous vascular permeability	Uneven nanoparticle accumulation	Active targeting and vascular normalization
Dense extracellular matrix	Restricted tumor penetration	ECM degradation and stromal modulation

Elevated interstitial fluid pressure	Reduced extravasation and diffusion	Pressure normalization strategies
Protein corona formation	Altered biological identity and targeting	Surface engineering and biomimetic coatings
Macrophage uptake	Premature nanoparticle removal	Cell membrane camouflage and PEGylation
RES clearance	Reduced circulation time	Biomimetic nanocarriers and stealth nanoparticles
Low tumor accumulation (<1%)	Limited therapeutic efficacy	AI-guided design, stimuli-responsive systems, and personalized nanomedicine

6. Beyond the EPR Effect: Intelligent Targeting Strategies

The limitations of the Enhanced Permeability and Retention (EPR) effect have prompted the development of **intelligent targeting strategies** that improve nanoparticle delivery through active recognition of cancer cells and controlled drug release. Unlike first-generation nanocarriers that rely mainly on passive accumulation, these advanced systems are designed to overcome biological barriers, enhance tumor specificity, and maximize therapeutic efficacy while minimizing systemic toxicity. The integration of molecular targeting, stimuli-responsive drug release, and multifunctional nanotechnology has significantly improved the clinical potential of cancer nanomedicine (Mitragotri et al., 2021; Jain and Stylianopoulos, 2023).

6.1 Active Targeting

Active targeting involves the functionalization of nanoparticle surfaces with specific ligands that recognize and bind to overexpressed receptors on cancer cells or within the tumor microenvironment. Common targeting ligands include monoclonal antibodies, peptides, aptamers, folic acid, transferrin, and carbohydrates. After binding to their target receptors, nanoparticles are internalized through receptor-mediated endocytosis, resulting in higher intracellular drug concentrations and improved therapeutic outcomes compared with passive targeting alone (Shi et al., 2022; Blanco et al., 2023). Monoclonal antibodies offer excellent specificity toward tumor-associated antigens such as HER2, EGFR, and CD44, whereas peptide ligands provide advantages such as smaller size, lower immunogenicity, and easier synthesis. Aptamers and folate-conjugated nanoparticles have also shown promising results in selectively targeting cancer cells with minimal effects on healthy tissues. These ligand-based strategies enhance tumor selectivity and reduce off-target toxicity, making them valuable components of next-generation nanomedicines (Danhier, 2016; Kizhakkanoodan et al., 2024).

6.2 Stimuli-Responsive Nanocarriers

Stimuli-responsive nanocarriers are designed to release their therapeutic payload only after exposure to specific internal or external triggers. Endogenous stimuli include acidic pH, reactive oxygen species (ROS), enzymes, glutathione, and hypoxic conditions that are characteristic of the tumor microenvironment. Exogenous triggers such as light, ultrasound, magnetic fields, and heat can also be applied to achieve precise spatiotemporal drug release (Deng et al., 2022; Shi et al., 2022). Among these systems, **pH-responsive nanoparticles** are widely studied because the acidic tumor environment promotes rapid drug release while maintaining stability under physiological conditions. Similarly, enzyme-responsive and ROS-sensitive nanocarriers exploit biochemical abnormalities within tumors to improve treatment specificity. These intelligent systems minimize premature drug leakage, enhance intratumoral drug concentration, and reduce systemic adverse effects (Blanco et al., 2023).

6.3 Multifunctional and Intelligent Nanoplatforms

Recent advances have led to the development of multifunctional nanoparticles capable of combining drug delivery, molecular imaging, photothermal therapy, photodynamic therapy, immunotherapy, and gene delivery within a single platform. These **theranostic nanocarriers** enable simultaneous diagnosis and treatment, allowing clinicians to

monitor therapeutic response in real time while improving treatment precision. Such integrated systems represent an important step toward personalized oncology (Mitragotri et al., 2021; Gomerdinger et al., 2025). The incorporation of **artificial intelligence (AI)** and machine learning has further accelerated nanoparticle design by predicting optimal physicochemical properties, biodistribution, drug loading efficiency, and patient-specific therapeutic responses. AI-assisted optimization reduces experimental time and supports the development of precision nanomedicine tailored to individual tumor characteristics (Samathoti et al., 2025).

Future intelligent targeting strategies are expected to integrate active targeting, biomimetic engineering, stimuli-responsive drug delivery, artificial intelligence, and personalized medicine into a single adaptive platform. Cell membrane-coated nanoparticles, exosome-inspired carriers, and AI-guided nanocarriers are likely to overcome many of the limitations associated with passive EPR-based delivery. By addressing tumor heterogeneity and biological barriers, these next-generation systems have the potential to improve clinical translation and establish precision nanomedicine as a standard approach in cancer therapy (Jain and Stylianopoulos, 2023; Gomerdinger et al., 2025).

FUTURE PERSPECTIVE

Table 5. Intelligent Targeting Strategies Beyond the EPR Effect

Strategy	Mechanism	Major Advantages
Active targeting	Ligand–receptor interaction	Enhanced tumor specificity and cellular uptake
Antibody-mediated targeting	Recognition of tumor-specific antigens	High targeting accuracy
Peptide and aptamer targeting	Receptor-mediated endocytosis	Improved selectivity and reduced immunogenicity
Stimuli-responsive nanoparticles	Triggered drug release (pH, ROS, enzymes, heat, ultrasound)	Controlled and site-specific drug delivery
Multifunctional nanoplatforms	Combined imaging and therapy	Simultaneous diagnosis and treatment
AI-assisted nanoparticle design	Computational optimization	Personalized and precision nanomedicine

7. Biomimetic Nanomedicine: Mimicking Nature for Precision Cancer Therapy

Biomimetic nanomedicine has emerged as one of the most promising strategies to overcome the limitations of conventional nanocarriers. Unlike synthetic nanoparticles that are rapidly recognized and eliminated by the immune system, biomimetic nanoparticles incorporate natural biological components such as cell membranes, extracellular vesicles, or biomolecules to mimic the physiological properties of living cells. This approach enhances biocompatibility, prolongs systemic circulation, improves tumor targeting, and reduces immune clearance. By integrating the advantages of natural biological systems with engineered nanomaterials, biomimetic nanomedicine represents a major advancement toward precision cancer therapy (Fang et al., 2018; Zhang et al., 2021).

7.1 Cell Membrane-Coated Nanoparticles

Cell membrane-coated nanoparticles are among the most extensively studied biomimetic systems. In this strategy, synthetic nanoparticles are coated with membranes derived from red blood cells (RBCs), platelets, leukocytes, stem cells, or cancer cells, allowing them to inherit the biological functions of their source cells. These biomimetic coatings reduce immune recognition, prolong blood circulation, and improve tumor-specific accumulation (Hu et al., 2019; Fang et al., 2023). Red blood cell (RBC) membrane-coated nanoparticles exhibit prolonged circulation because RBC membranes express CD47, a "don't eat me" signal that suppresses macrophage-

mediated phagocytosis. Platelet membrane-coated nanoparticles preferentially interact with damaged blood vessels and circulating tumor cells, enhancing metastatic tumor targeting. Cancer cell membrane-coated nanoparticles utilize homotypic adhesion molecules to selectively bind tumors of the same origin, improving targeting specificity. Similarly, immune cell membrane-coated nanoparticles, including macrophage- and leukocyte-derived systems, effectively penetrate inflamed tumor tissues and modulate the tumor immune microenvironment (Chen et al., 2022; Fang et al., 2023).

7.2 Exosome-Based Nanomedicine

Exosomes are naturally secreted extracellular vesicles with diameters of approximately 30–150 nm that mediate intercellular communication by transporting proteins, lipids, messenger RNA, and microRNA. Their excellent biocompatibility, low immunogenicity, and intrinsic targeting ability make them attractive drug delivery vehicles. Engineered exosomes have demonstrated considerable potential for delivering chemotherapeutic agents, nucleic acids, CRISPR components, and immunotherapeutic molecules directly to tumor cells while minimizing systemic toxicity (Kalluri and LeBleu, 2020; Pegtel and Gould, 2019). Despite their therapeutic advantages, large-scale production, purification, cargo loading efficiency, and quality standardization remain major challenges for clinical translation. Continued improvements in exosome engineering and manufacturing are expected to accelerate their application in precision oncology (Li et al., 2024).

7.3 Hybrid Biomimetic Nanocarriers

Hybrid biomimetic nanoparticles combine natural biological membranes with synthetic nanomaterials to achieve multifunctional therapeutic performance. These systems integrate the immune-evasive properties of biological membranes with the structural stability, high drug-loading capacity, and controlled release characteristics of engineered nanoparticles. Hybrid platforms are increasingly being investigated for combination therapies involving chemotherapy, photothermal therapy, immunotherapy, and gene therapy (Zhang et al., 2021; Shi et al., 2022).

7.4 Clinical Potential and Future Perspectives

Biomimetic nanomedicine has significantly expanded the possibilities for targeted cancer therapy by addressing major biological barriers such as immune clearance, poor tumor penetration, and limited circulation time. Current research is focused on combining **biomimetic engineering**, **stimuli-responsive drug delivery**, **artificial intelligence**, and **personalized medicine** to develop adaptive nanocarriers capable of responding to individual tumor characteristics. Although challenges related to manufacturing, reproducibility, regulatory approval, and long-term safety remain, biomimetic nanoparticles are expected to play a central role in the next generation of precision oncology (Blanco et al., 2023; Gomerdinger et al., 2025).

Table 6. Types of Biomimetic Nanocarriers Used in Cancer Therapy

Biomimetic System	Source	Major Advantages	Applications
RBC membrane-coated nanoparticles	Red blood cells	Immune evasion, prolonged circulation	Chemotherapy, drug delivery
Platelet membrane-coated nanoparticles	Platelets	Tumor vascular targeting, metastasis inhibition	Targeted chemotherapy
Cancer cell membrane-coated nanoparticles	Tumor cells	Homologous tumor targeting	Precision drug delivery
Leukocyte/macrophage-coated nanoparticles	Immune cells	Tumor penetration, immune modulation	Immunotherapy
Exosome-based nanocarriers	Extracellular vesicles	Natural targeting, low immunogenicity	Drug delivery, gene therapy
Hybrid biomimetic nanoparticles	Cell membranes + synthetic nanoparticles	Multifunctionality, controlled release	Theranostics and combination therapy

8. Artificial Intelligence and Precision Nanomedicine

Artificial intelligence (AI) is rapidly transforming cancer nanomedicine by enabling the rational design, optimization, and personalization of nanoparticle-based drug delivery systems. Traditional nanoparticle development often relies on time-consuming experimental screening and trial-and-error approaches. In contrast, AI integrates machine learning (ML), deep learning (DL), and big data analytics to predict nanoparticle behavior, optimize physicochemical properties, and accelerate the development of effective nanotherapeutics. The convergence of AI with nanotechnology is shifting cancer treatment from generalized drug delivery toward **precision nanomedicine**, where therapeutic strategies are tailored to the biological characteristics of individual patients (Mamoshina et al., 2021; Samathoti et al., 2025).

8.1 AI-Assisted Nanoparticle Design

Machine learning algorithms can analyze large experimental datasets to predict the influence of nanoparticle size, shape, surface charge, composition, and drug loading on biodistribution, cellular uptake, and therapeutic efficacy. These computational models reduce experimental workload, shorten formulation development time, and improve the selection of optimized nanocarriers with enhanced tumor-targeting efficiency (Kizhakkanoodan et al., 2024; Gomerdinger et al., 2025). AI also facilitates the identification of optimal ligand combinations for active targeting and assists in designing multifunctional nanoparticles capable of delivering chemotherapeutic agents, nucleic acids, proteins, or imaging probes simultaneously. Such predictive modeling enhances formulation reproducibility while minimizing development costs (Mitragotri et al., 2021).

8.2 Precision Medicine and Personalized Therapy

Precision nanomedicine combines AI with genomic, proteomic, transcriptomic, and metabolomic information to develop patient-specific therapeutic strategies. By integrating multi-omics data with clinical information, AI can identify molecular biomarkers, predict treatment response, and recommend the most suitable nanoparticle formulation for individual patients. This personalized approach improves therapeutic efficacy while reducing unnecessary toxicity associated with conventional chemotherapy (Topol, 2019; Blanco et al., 2023). Furthermore, AI supports early diagnosis, patient stratification, prognosis prediction, and real-time monitoring of therapeutic outcomes, enabling clinicians to modify treatment regimens according to disease progression and individual response.

8.3 AI in Drug Delivery and Clinical Translation

AI has become an important tool for predicting nanoparticle pharmacokinetics, biodistribution, toxicity, and drug release profiles before clinical evaluation. Digital modeling and computational simulations help identify potential formulation failures during the early stages of development, thereby increasing the efficiency of preclinical research. AI-assisted image analysis also improves tumor detection, nanoparticle tracking, and treatment monitoring using advanced imaging modalities such as magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET) (Esteva et al., 2021; Gomerdinger et al., 2025). Despite these advances, several challenges remain, including limited availability of high-quality datasets, algorithm transparency, regulatory acceptance, data privacy, and ethical considerations. Addressing these issues will be essential for the successful integration of AI into routine clinical oncology.

8.4 Future Perspectives

The future of cancer nanomedicine lies in the integration of **artificial intelligence, biomimetic engineering, multi-omics technologies, digital pathology, and precision medicine**. Emerging concepts such as digital twins, autonomous nanoparticle optimization, and AI-guided treatment planning have the potential to revolutionize cancer therapy by enabling highly personalized and adaptive drug delivery systems. Continued collaboration among clinicians, data scientists, pharmaceutical researchers, and regulatory agencies will be essential to translate these innovations into clinical practice (Samathoti et al., 2025; Gomerdinger et al., 2025).

Table 7. Applications of Artificial Intelligence in Cancer Nanomedicine

AI Application	Role in Nanomedicine	Clinical Benefit
Machine learning	Optimization of nanoparticle formulation	Faster and more efficient formulation development
Deep learning	Prediction of nanoparticle behavior	Improved tumor targeting and drug delivery
Multi-omics integration	Patient-specific treatment planning	Personalized precision medicine
Medical image analysis	Tumor detection and nanoparticle tracking	Enhanced diagnosis and treatment monitoring
Predictive toxicity models	Safety assessment	Reduced adverse effects and development costs
Digital twins	Simulation of therapeutic response	Individualized treatment optimization

9. Clinical Translation of Cancer Nanomedicine: Opportunities and Challenges

Despite remarkable progress in nanoparticle engineering and targeted drug delivery, the successful **clinical translation** of cancer nanomedicine remains a significant challenge. Over the past three decades, thousands of nanoparticle formulations have demonstrated promising results in laboratory studies; however, only a limited number have received regulatory approval for clinical use. This gap between preclinical success and clinical application highlights the complexity of translating nanomedicine from the research laboratory to patient care (Wilhelm et al., 2016; Hare et al., 2017).

9.1 Clinically Approved Nanomedicines

Several nanoparticle-based formulations have successfully entered clinical practice and demonstrated improved safety compared with conventional chemotherapy. **Doxil® (liposomal doxorubicin)** was the first FDA-approved nanomedicine for cancer treatment and significantly reduced cardiotoxicity associated with free doxorubicin. Similarly, **Abraxane® (albumin-bound paclitaxel)** improved drug solubility and eliminated the need for toxic solvents, enhancing treatment tolerability. Other approved formulations, including liposomal irinotecan (Onivyde®) and liposomal daunorubicin, further demonstrate the clinical potential of nanotechnology in oncology (Barenholz, 2012; Shi et al., 2022). Although these products represent important milestones, most approved nanomedicines still rely primarily on passive drug delivery rather than advanced intelligent targeting strategies.

9.2 Challenges in Clinical Translation

One of the major obstacles to clinical translation is the **biological heterogeneity of human tumors**. Differences in tumor vascularization, extracellular matrix composition, immune responses, and patient genetics significantly influence nanoparticle accumulation and therapeutic efficacy. Consequently, formulations that perform well in animal models often fail to achieve similar outcomes in human clinical trials (Lammers et al., 2024). Large-scale manufacturing also presents considerable challenges. Maintaining consistent nanoparticle size, surface charge, drug loading efficiency, and long-term stability during industrial production is technically demanding. Small variations in manufacturing conditions may substantially alter nanoparticle behavior, affecting safety and therapeutic performance (Mitragotri et al., 2021). In addition, **protein corona formation**, rapid clearance by the mononuclear phagocyte system (MPS), limited tumor penetration, and variability in the Enhanced Permeability and Retention (EPR) effect continue to reduce treatment efficiency. These biological barriers emphasize the need for more intelligent and adaptive nanoparticle designs (Sindhwani et al., 2020).

9.3 Regulatory and Safety Considerations

Regulatory approval of nanomedicines requires comprehensive evaluation of their quality, safety, efficacy, pharmacokinetics, biodistribution, immunogenicity, and long-term toxicity. Unlike

conventional pharmaceuticals, nanomedicines possess unique physicochemical properties that may alter their biological interactions, requiring specialized characterization methods and standardized manufacturing protocols. Regulatory agencies, including the **U.S. Food and Drug Administration (FDA)** and the **European Medicines Agency (EMA)**, continue to refine guidelines for evaluating nanoparticle-based therapeutics (Ventola, 2017; Gomerdinger et al., 2025). Long-term biosafety remains another important concern. Although many nanocarriers are biodegradable, some inorganic nanoparticles may accumulate in vital organs, raising questions regarding chronic toxicity and environmental impact. Therefore, comprehensive toxicological studies are essential before widespread clinical application.

9.4 Future Outlook

Future clinical translation will increasingly depend on integrating **biomimetic nanotechnology**, **artificial intelligence**, **precision medicine**, and **quality-by-design (QbD)** approaches into nanoparticle development. Patient-derived tumor models, organoids, tumor-on-a-chip platforms, and AI-assisted predictive modeling are expected to improve the selection and optimization of nanomedicines before clinical trials. These technologies may significantly reduce development costs, enhance clinical success rates, and accelerate regulatory approval (Blanco et al., 2023; Samathoti et al., 2025). Continued collaboration among pharmaceutical scientists, clinicians, engineers, and regulatory authorities will be essential to overcome current translational barriers. With ongoing advances in biomaterials, computational biology, and personalized medicine, next-generation nanotherapeutics are expected to provide safer, more effective, and individualized treatment options for cancer patients.

Table 8. Major Challenges and Future Solutions for Clinical Translation of Cancer Nanomedicine

Challenge	Impact	Potential Solution
Tumor heterogeneity	Variable therapeutic response	Personalized nanomedicine and biomarker-guided therapy
Poor clinical translation	Limited success in human trials	Patient-derived models and organoids
Protein corona formation	Reduced targeting efficiency	Surface engineering and biomimetic coatings
MPS/RES clearance	Short circulation time	Cell membrane-coated nanoparticles and stealth nanocarriers
Manufacturing variability	Inconsistent product quality	Quality-by-Design (QbD) and standardized production
Regulatory complexity	Delayed approval	Harmonized regulatory guidelines
Long-term toxicity	Safety concerns	Biodegradable and biocompatible nanomaterials
High development cost	Limited commercialization	AI-assisted formulation optimization and scalable manufacturing

CONCLUSION

Cancer nanomedicine has undergone a remarkable transformation over the past decade, evolving from conventional nanoparticle-based drug delivery systems to intelligent, biomimetic, and precision-guided therapeutic platforms. Early nanomedicines primarily relied on the Enhanced Permeability and Retention (EPR) effect to achieve passive tumor targeting and successfully improved the pharmacokinetic profile and safety of several anticancer drugs. However, increasing clinical evidence has demonstrated that the EPR effect alone is insufficient to ensure consistent nanoparticle accumulation in human tumors because of tumor heterogeneity, abnormal vascular architecture, dense extracellular matrix, elevated interstitial fluid pressure, protein corona formation, and rapid immune clearance. These limitations have led to the emergence of the **EPR paradox**, fundamentally

reshaping the current understanding of nanoparticle-mediated drug delivery (Wilhelm et al., 2016; Sindhwani et al., 2020; Jain and Stylianopoulos, 2023). To overcome these biological barriers, cancer nanomedicine has progressively shifted toward intelligent targeting strategies that combine active ligand-mediated targeting, stimuli-responsive drug release, biomimetic engineering, and tumor microenvironment modulation. Biomimetic nanocarriers, including cell membrane-coated nanoparticles and exosome-inspired delivery systems, have demonstrated significant potential to improve immune evasion, prolong systemic circulation, and enhance tumor-specific drug delivery. Simultaneously, advances in artificial intelligence, machine learning, and multi-omics technologies are enabling the rational design of personalized nanomedicines capable of optimizing drug delivery according to the molecular characteristics of individual patients (Fang et al., 2023; Kizhakkanoodan et al., 2024; Samathoti et al., 2025). Despite these advances, several challenges continue to hinder the clinical translation of nanomedicine, including manufacturing reproducibility, regulatory complexity, long-term safety, biological variability, and the limited predictive value of conventional preclinical models. Addressing these challenges will require multidisciplinary collaboration among pharmaceutical scientists, clinicians, biomedical engineers, computational scientists, and regulatory authorities. The adoption of patient-derived tumor models, organ-on-a-chip technologies, quality-by-design (QbD) approaches, and AI-assisted predictive modeling is expected to accelerate the successful translation of next-generation nanotherapeutics into clinical practice (Mitragotri et al., 2021; Gomerdinger et al., 2025). In conclusion, the field of cancer nanomedicine is undergoing a paradigm shift from passive nanoparticle accumulation toward adaptive, intelligent, and patient-centered therapeutic systems. The future of precision oncology lies in integrating biomimetic nanotechnology, artificial intelligence, stimuli-responsive materials, and personalized medicine to develop smart nanocarriers capable of overcoming complex tumor barriers and delivering highly effective, individualized cancer therapy. Continued innovation in these areas is expected to bridge the gap between experimental research and clinical application, ultimately improving treatment outcomes, reducing systemic toxicity, and advancing the next generation of precision cancer therapeutics.

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