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Bridging the Translational Gap in Cancer Nanomedicine: A Systematic Review of Preclinical Benefits and Clinical Challenges

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Abstract

Introduction: Despite notable advancements in cancer therapy, conventional treatments continue to face significant limitations, including nonspecific distribution, systemic toxicity, and frequent therapeutic failure due to drug resistance. Nanomedicine has emerged as a promising alternative by enabling targeted delivery of chemotherapeutics through engineered nanoscale carriers that improve drug solubility, stability, and selective accumulation in tumors. Although numerous preclinical studies report enhanced efficacy and reduced toxicity using nanoparticles in animal models, only a small number of these systems have succeeded in clinical translation.

Methods: This systematic review assessed the therapeutic efficacy of nanoparticle-based cancer treatments in animal models and examined the translational challenges preventing their successful implementation in humans. Forty peer-reviewed studies published between 2004 and 2025 were selected from academic databases including PubMed, Scopus, ScienceDirect, Nature, SpringerLink, and Frontiers. Studies were included based on the use of nanoparticles in preclinical cancer models with reported outcomes on efficacy, toxicity, or clinical development status.

Results: Preclinical investigations consistently demonstrated that nanoparticle systems, including liposomes, polymeric carriers, inorganic particles, and stimuli-responsive platforms, improve tumor accumulation, reduce off-target toxicity, and induce stronger therapeutic responses than conventional drugs. Active targeting strategies, such as ligand-mediated or tumor microenvironment-responsive designs, further enhanced selectivity and efficacy. However, less than 1% of the injected nanoparticle dose typically reaches solid tumors in human patients. This stark discrepancy arises from biological and technical barriers, including poor predictive power of animal models, rapid immune clearance, tumor heterogeneity, manufacturing complexities, and regulatory constraints.

Discussion: The findings underscore the limitations of current preclinical tools in forecasting clinical outcomes. While existing platforms show potent antitumor activity in animals, their clinical benefit is limited unless designs account for human-specific pharmacokinetics and immunological responses. Innovations such as humanized models, biomarker-guided patient selection, and artificial intelligence-driven nanoparticle optimization are beginning to address these issues.

Conclusion: To unlock the clinical potential of nanomedicine, future development must integrate advanced preclinical systems, precision targeting, and interdisciplinary collaboration. This review highlights the critical gaps and offers a roadmap toward more effective and translatable nanotherapeutic strategies in cancer care.

Keywords: cancer nanomedicine; targeted drug delivery; clinical translation; nanoparticle therapeutics; tumor microenvironment

Introduction

Cancer remains a leading cause of morbidity and mortality worldwide, with global incidence and death rates continuing to rise despite decades of therapeutic advancement [1]. Conventional treatment modalities such as chemotherapy and radiation lack selectivity, cause systemic toxicity, and often lead to the development of drug resistance [2]. These disadvantages underscore an urgent need for more effective and targeted therapeutic approaches.

Nanomedicine, the application of nanoscale materials in disease diagnosis and treatment, has gained increasing attention as a promising approach to overcome some of these limitations in cancer therapy. Nanoparticles are typically defined as engineered structures with dimensions between 1 and 100 nm, a size range that imparts unique physicochemical properties such as high surface-to-volume ratio and tunable surface chemistry, which can be exploited for more precise drug delivery [3]. Engineered nanoparticles offer numerous advantages as drug carriers,

including improved drug solubility, extended circulation time, controlled drug release, and greater accumulation in tumor tissue via the enhanced permeability and retention (EPR) effect [4, 5]. In particular, these nanoparticles can bypass biological barriers and deliver chemotherapeutic agents directly to tumor cells, which helps reduce off-target toxicity and improve therapeutic outcomes [6].

Over the past decade, many preclinical studies have demonstrated that a variety of nanocarriers - including liposomes, polymeric nanoparticles, and inorganic materials - can enhance drug delivery, reduce systemic toxicity, and increase tumor-specific drug accumulation in vivo [7, 8, 9]. Notably, these nanoparticle systems have produced significant tumor regression and improved survival in animal models compared to administering the free drugs alone [7]. Collectively, such findings contribute to a growing body of evidence that nanotechnology can improve therapeutic outcomes in oncology.

However, translating these preclinical successes into clinical treatments has proven extremely challenging. A comprehensive analysis by Wilhelm et al. (2016) showed that less than 1% of administered nanoparticles actually reach solid tumors in human patients, revealing a stark gap between the promise of preclinical studies and clinical reality [10, 11]. Moreover, very few nanoparticle-based drugs have been approved by the FDA, with only a handful (such as Doxil and Abraxane) reaching the market to date [12, 13]. This shortfall is due to multiple challenges, including clearance by the immune system, tumor heterogeneity, difficulties in scaling up nanoparticle production, and regulatory complexities [3, 13, 14].

Given these translational barriers, it is important to examine which nanoparticle design features or preclinical outcomes actually correlate with later clinical success or failure. This review aims to systematically analyze peer-reviewed literature to identify patterns in nanoparticle design, targeting strategies, and therapeutic performance in preclinical cancer models, while also tracing the fate of these nanomedicines in clinical development. Beyond mapping current trends, this review also critically discusses key advancements, persistent challenges, and emerging directions for future research in the field of cancer nanomedicine. A better understanding of this translational gap is crucial for optimizing future nanotherapeutic platforms and increasing their chances of successful clinical implementation [15, 16].

Methods

A systematic literature review was conducted to evaluate the therapeutic potential of nanoparticle-based cancer treatments in preclinical models and to identify barriers to clinical translation. Articles were retrieved from six academic databases: PubMed, Scopus, ScienceDirect, Nature, SpringerLink, and Frontiers, using keyword combinations such as “cancer”, “nanoparticles”, “preclinical”, “animal model”, “clinical trial”, and “translation.” The search was limited to English-language, peer-reviewed articles published between 2004 and 2025.Studies were included if they used nanoparticles in preclinical animal cancer models and reported outcomes related to efficacy, toxicity, targeting strategies, or clinical relevance. Exclusion criteria comprised in vitro-only studies, non-cancer applications, and non-original articles (e.g., editorials, protocols, or incomplete reports). After screening, 40 articles met the criteria and were included for full-text analysis.

Results

Nanoparticle Classes in Preclinical Cancer Research

A wide range of nanoparticle platforms have been explored in preclinical cancer models, each offering distinct structural and functional advantages:

Liposomes, such as Doxil, are phospholipid-based vesicles that encapsulate drugs within aqueous or lipid compartments. They are biocompatible and can reduce toxicity while enhancing tumor uptake [12, 17, 18].

Polymeric nanoparticles, especially those based on PLGA and PEG, offer biodegradable, modifiable surfaces suitable for prolonged circulation and sustained release. They are often engineered to avoid immune clearance and can be tailored for multi-drug loading and targeted delivery [4, 19].

Inorganic nanoparticles (such as gold, silica, or iron oxide) are rigid and precisely engineerable, enabling dual functionality in therapy and imaging. Gold nanoparticles provide photothermal capabilities, while iron oxide systems serve as magnetic resonance imaging (MRI) contrast agents [1, 6, 20].

Stimuli-responsive systems release drugs in response to internal signals (like pH or ROS) or external triggers (heat, light, magnetism), allowing on-site activation and reducing off-target effects [8, 21]. Some designs also activate programmed cell death pathways such as apoptosis or ferroptosis, enhancing efficacy even in resistant tumors [22].

Hybrid nanoparticles combine different materials to maximize drug loading, stability, and targeting. Lipid-polymer or liposome-metal hybrids enable simultaneous therapy and imaging, with synergistic results in mouse models [9, 15].

Dendrimers, though less common, are highly branched polymers capable of precise targeting and high drug payloads. When functionalized with ligands like folate or transferrin, dendrimers have demonstrated marked tumor regression in vivo [19].

These classes represent the diverse engineering strategies used to optimize nanoparticle performance in preclinical cancer therapy.

Preclinical Therapeutic Benefits of Nanoparticles

A wide range of preclinical studies have demonstrated that nanocarriers significantly outperform conventional

chemotherapy in terms of efficacy, biodistribution, and toxicity profiles. Unlike free drugs, which often exhibit poor pharmacokinetics and high systemic toxicity, nanoparticles are designed to optimize delivery through features such as high surface-area-to-volume ratios, tunable surface chemistry, and capacity to encapsulate both hydrophilic and hydrophobic drugs [2, 4]. These structural characteristics translate into prolonged circulation, improved plasma stability, and increased tumor accumulation through the EPR effect, as confirmed in multiple murine models [5, 8].

Beyond biodistribution, therapeutic outcomes in animal studies consistently report superior tumor suppression and survival rates when using nanoparticle-based formulations. For example, paclitaxel or doxorubicin encapsulated in polymeric or liposomal nanocarriers induced significantly higher levels of apoptosis, slowed tumor progression, and extended survival compared to the free-drug equivalents [7, 8, 17, 18]. Notably, liposomal doxorubicin (Doxil) reduced cardiotoxicity without compromising antitumor efficacy - an effect attributed to the shielding of normal tissues through PEGylation and controlled drug release [17, 18, 23].

Several studies also report the ability of nanocarriers (mostly polymeric) to bypass multidrug resistance mechanisms, such as P-glycoprotein-mediated efflux, by enabling intracellular accumulation and sustained cytotoxic exposure [9, 15]. In some cases, a single injection led to sustained tumor suppression, indicating a long-acting effect [7]. Additionally, many platforms, such as polymeric micelles, liposomes, hybrid systems, and dendrimers, support combinatorial delivery, enabling co-encapsulation of drugs or concurrent release of chemotherapy and immunomodulatory agents [19].

In addition to small molecules, nanoparticles deliver small interfering RNA (siRNA) and microRNA (miRNA) to silence oncogenes or modulate immunity with high selectivity and minimal off-target effects [19, 21]. For example, polymer-based nanoparticles carrying siRNA against an autophagy-related gene enhanced the efficacy of doxorubicin and suppressed tumor growth in a triple-negative breast cancer mouse model [24]. Some preclinical systems also integrate imaging and therapeutic components, enabling real-time monitoring of treatment - an approach known as theranostics [1, 9]. A representative example is a perfluorocarbon–polyepinephrine nanoparticle that simultaneously provided ultrasound and fluorescent tumor imaging while delivering photothermal and chemodynamic therapy under near-infrared light, leading to pronounced tumor regression in vivo [25].

Together, these systems improve tumor selectivity, circulation times, and resistance bypassing, while allowing for multifunctional and long-acting treatment. Though these outcomes are largely limited to animal models, they highlight the broad therapeutic potential of nanomedicine.

Targeting Strategies in Preclinical Models

In preclinical cancer nanomedicine, passive targeting via the EPR effect remains a key delivery mechanism. Leaky tumor vasculature and poor lymphatic drainage allow nanoparticles to accumulate more readily in tumor tissue than in healthy organs [4, 5]. While this has driven many successes in animal models, EPR-driven delivery alone often suffers from heterogeneous and suboptimal distribution. Tumor size, vascular density, and stromal factors (e.g. high interstitial pressure and dense extracellular matrix) can hinder uniform nanoparticle distribution, leading to variable drug exposure across tumor sites [15, 26]. In some cases, passive targeting alone results in suboptimal or nonspecific dispersion, prompting the development of enhanced targeting strategies.

Active targeting improves tumor specificity by functionalizing nanoparticles with ligands that bind cancer-associated receptors. These ligands, such as antibodies, peptides, aptamers, or small molecules like folic acid, enable receptor-mediated uptake into tumor cells [5, 9]. For example, Cetuximab (an anti-epidermal growth factor receptor (EGFR) antibody) conjugation enables nanoparticles to bind selectively to EGFR-overexpressing tumor cells, achieving higher tumor accumulation and uptake while sparing normal cells lacking the target [15]. Similarly, peptide-tagged (e.g. RGD-decorated nanoparticles) and aptamer-functionalized carriers have demonstrated improved tumor inhibition in mouse models, outperforming non-targeted versions. Overall, active targeting has become central in preclinical studies, often yielding greater tumor specificity and efficacy than passive targeting alone [7, 9].

Efforts are also underway to target specific cell types or subcellular compartments. Nanoparticles can be engineered with signals that direct them to organelles like mitochondria or nuclei, enhancing intracellular drug delivery. Mitochondria-targeting carriers, for example, can trigger apoptosis by inducing oxidative stress at the site of energy production- an approach that has shown promising antitumor effects in animal models [5, 15]. Although organelle-level targeting remains technically challenging in vivo, it represents a frontier in precision therapy design.

Another promising strategy involves exploiting the tumor microenvironment (TME). Tumors create distinct physiological conditions, such as acidic pH, hypoxia, high reducing-agent levels, and tumor-specific enzymes that can trigger controlled drug release. TME-responsive nanoparticles are designed to remain stable in circulation but to release their payload in response to tumor-localized triggers. pH-sensitive or enzyme-sensitive carriers, for instance, destabilize in acidic or enzyme-rich environments, ensuring site-specific delivery. Likewise, nanocarriers sensitive to glutathione or matrix metalloproteinases can unload drugs preferentially within the tumor's milieu. Such delivery not only intensifies the drug action at the cancer

site but also minimizes collateral toxicity to healthy cells [8, 21].

Preclinical cancer models demonstrate that combining passive EPR accumulation with active ligand targeting and TME-responsive release results in better tumor specificity and therapeutic outcomes [5, 9, 15]. These multilayered targeting strategies are central to advancing precision nanotherapy in oncology.

Translational Barriers and Clinical Outcomes of Nanoparticle Therapies

Despite strong preclinical results, many nanoparticle systems struggle to show the same efficacy in clinical settings. One major issue is the discrepancy in drug delivery between animal models and humans. While the EPR effect enables nanoparticles to accumulate efficiently in tumors in mice, this process is much less predictable in human cancers [5, 13]. A meta-analysis by Wilhelm et al. (2016) showed that, on average, less than 1% of an injected nanoparticle dose reaches solid tumors in patients [10, 11]. Tumor variability - differences in vascular permeability, pressure, and extracellular matrix density - further complicates delivery, making it difficult to predict human outcomes from animal data [8, 13, 26]. As a result, traditional animal models may overestimate nanoparticle efficacy and fail to reflect the complexity of human disease.

Another major challenge is immune clearance. Once administered, nanoparticles are often opsonized by plasma proteins and rapidly cleared by the mononuclear phagocyte system, particularly by Kupffer cells in the liver and spleen macrophages [27, 28]. This limits their circulation time and tumor-targeting efficiency. Although PEGylation can help reduce immune detection by creating "stealth" nanoparticles, this strategy does not completely prevent clearance [4, 23]. Moreover, repeated dosing of PEGylated nanoparticles can induce the Accelerated Blood Clearance (ABC) phenomenon, in which anti-PEG antibodies mediate rapid immune recognition and clearance, thereby compromising efficacy [29].

Tumor heterogeneity and biological variability across patients further impede translation [30, 31]. Solid tumors in different patients can differ dramatically in blood vessel density, permeability, and receptor expression [26]. This variability leads to uneven nanoparticle distribution and therapeutic response in clinical settings [13, 30, 32]. For instance, well-perfused tumors may absorb nanoparticles efficiently, while dense or poorly vascularized tumors may block them entirely [26, 33]. Clinical trials have reported large differences in drug accumulation even among patients treated with the same nanodrug [31]. Such unpredictability means that a nanoparticle delivery system must be robust across a range of tumor microenvironments - a criterion few current platforms meet.

In addition to biological challenges, technical and manufacturing hurdles further restrict clinical translation. Scaling up nanoparticle production while maintaining quality and reproducibility is complex. Minor variations in synthesis, such as mixing speed or solvent composition, can affect particle size, drug content, or surface properties, impacting performance [34, 35]. These issues are especially pronounced for complex hybrid or multifunctional nanoparticles, which may require intricate assembly steps and specialized materials [14]. Giri et al. (2023) noted that despite therapeutic promise, the clinical translation of many nanodrugs is hindered by challenges in large-scale manufacturing, reproducibility, and cost.

Regulatory challenges also play a major role. Nanomedicines require detailed physicochemical and toxicological characterization, which prolongs development timelines and increases costs [36]. Without early clinical signals of efficacy, developers and investors may hesitate to support such high-risk platforms, especially those without clear advantages over conventional treatments [37].

Despite these setbacks, a few nanoparticle-based drugs have successfully navigated this landscape. The most well-known examples - Doxil (PEGylated liposomal doxorubicin) and Abraxane (albumin-bound paclitaxel) - have achieved regulatory approval and widespread clinical use. Doxil prolongs circulation and promotes tumor accumulation while lowering the cardiotoxicity typically seen with free doxorubicin [17, 18]. Abraxane, by using albumin nanoparticles instead of toxic solvents like Cremophor EL, increases tolerability and allows higher dosing [38]. These benefits are largely due to pharmacokinetics enhancements (extended half-life, improved tumor delivery) and lower off-target toxicity, features that helped early-generation nanodrugs gain approval based on reduced adverse effects while maintaining efficacy [8].

In contrast, many investigational nanotherapies have failed to demonstrate added clinical value. Platforms featuring complex targeting ligands or multifunctional capabilities often fell short in efficacy or suffered from immune clearance issues in humans, despite excellent results in preclinical studies [27, 28, 29, 30, 31]. This pattern reveals a mismatch between scientific innovation and clinical practicality.

Taken together, these findings emphasize that for nanomedicines to succeed clinically, they must go beyond strong preclinical performance. They must also offer tangible advantages in human pharmacokinetics, manufacturability, safety, and cost-effectiveness. Without this alignment, even the most promising platforms risk joining the long list of failed candidates.

Discussion

Preclinical investigations consistently show that nanoparticles leverage the EPR effect, and when modified with targeting ligands, can achieve superior intratumoral drug accumulation and lower systemic toxicity, resulting in marked tumor regression in murine models [2, 4, 5, 7, 8]. However, a meta-analysis of 232 clinical and advanced

preclinical datasets revealed that, on average, only 0.7% of the injected nanoparticle dose reaches solid tumors in patients, a figure that has remained stagnant for over a decade [10, 11]. This disconnect highlights several interlinked barriers that continue to hinder clinical translation.

Model Limitations

Traditional two-dimensional cell cultures and murine xenograft models fail to mimic key features of human tumors, such as stromal density, vascular heterogeneity, and immune system complexity. As a result, essential nanoparticle-host interactions, including opsonization, complement activation, and endothelial transport, often emerge only during human trials [2, 3, 13, 14].

Biological Variability

Differences in vascular permeability, interstitial pressure, and extracellular matrix composition between and within patients produce inconsistent EPR effects. Additionally, nanoparticles are frequently diverted to clearance organs by the mononuclear phagocyte system or filtered by the kidneys, reducing tumor exposure [10, 11, 26, 27, 28].

Manufacturing and Regulation

The physical and chemical characteristics of nanoparticles are highly sensitive to fabrication parameters. Small changes in solvent composition, shear stress, or temperature can affect particle size, charge, and drug-release behavior - making large-scale manufacturing, batch consistency, and regulatory approval more difficult [3, 35, 36, 37].

These challenges explain why only a few formulations, most notably Doxil and Abraxane, have been successfully approved [17, 18, 38]. As a result, current clinical strategies focus on "smart" carriers that combine tumor-specific targeting with controlled, stimulus-responsive release. Examples include the prostate-specific membrane antigen (PSMA)-targeted polymeric nanoparticle BIND-014 and the thermosensitive liposome ThermoDox [39, 40].

To address the limitations of existing systems, three complementary approaches can be used:

1) Human-Relevant Experimental Models

Humanized mice, which are engrafted with patient-derived immune cells or tumor fragments, better replicate cytokine signaling, macrophage behavior, and nanoparticle distribution than conventional hosts [1, 3, 13]. Ex vivo models such as patient-derived organoids, tumor-on-a-chip platforms, and precision-cut tissue slices preserve tissue architecture and mechanical properties, allowing detailed evaluation of nanoparticle penetration and release while also identifying immunogenic or toxic properties early on [14, 21].

2) Biomarker-Guided Patient Selection

Screening for target receptor expression (e.g., PSMA, HER2, folate receptor) or for tumor microenvironmental features that favor EPR-based delivery can improve response rates in early clinical trials. This strategy has already enhanced outcomes in studies using targeted micelles and liposomes, while also generating valuable pharmacodynamic data to refine nanoparticle design [5, 8, 15, 26, 30].

3) Artificial Intelligence (AI) and Machine Learning

Predictive models trained on large datasets now link nanoparticle characteristics, such as size, shape, stiffness, and ligand density, to key outcomes like circulation time, tumor uptake, and endosomal escape. Generative algorithms can even suggest optimized designs before synthesis begins. At the clinical level, AI-enabled adaptive trial platforms are being used to adjust dosing based on real-time pharmacokinetics, imaging biomarkers, and toxicity signals, helping to detect efficacy earlier [16].

The success of these innovations will depend on continued collaboration across disciplines. Early involvement from academic researchers, manufacturing specialists, and regulatory agencies is essential to align nanoparticle design with real-world production and approval standards [12, 36]. Multidisciplinary advisory groups and flexible regulatory frameworks that allow protocol adjustments based on interim or real-world data could help accelerate progress [3, 7, 13]. Transparent communication between stakeholders from the design phase onward will be key to closing knowledge gaps and avoiding costly delays.

By integrating human-relevant modeling, biomarker-informed enrollment, AI-powered optimization, and collaborative regulatory strategies, the field of cancer nanomedicine can begin to overcome its current limitations. These combined efforts hold the potential to turn strong preclinical findings into safe, effective, and personalized cancer therapies.

Conclusions

This review synthesized evidence from seventeen peer-reviewed studies to examine the therapeutic promise of nanoparticles in preclinical cancer models and to explore the persistent obstacles hindering their clinical translation. Across a broad spectrum of nanoparticle types, animal studies demonstrated clear advantages: enhanced tumor-specific accumulation, reduced systemic toxicity, prolonged circulation, and improved treatment efficacy. Notably, advanced targeting strategies, such as ligand-mediated delivery and tumor microenvironment-responsive release, further refined precision in drug deployment. However, translation into human use has been constrained by several recurring issues: animal models often fail to mimic the complexity of human tumors, immune clearance mechanisms limit nanoparticle bioavailability, and production challenges complicate scale-up and regulatory compliance. Despite these setbacks, a few formulations like

Doxil and Abraxane have achieved clinical success, largely by solving specific pharmacological issues of their parent drugs. Future progress will likely depend on integrating human-relevant testing systems, biomarker-guided stratification, and AI-driven design to enhance predictive accuracy and streamline development. With greater interdisciplinary collaboration, the path forward for cancer nanomedicine holds real potential to turn preclinical innovation into meaningful clinical benefit.

List of Abbreviations
ABC: accelerated blood clearance
AI: artificial intelligence
EPR: enhanced permeability and retention
FDA: food and drug administration
HER2: human epidermal growth factor receptor 2
MRI: magnetic resonance imaging
PEG: polyethylene glycolPLGA – poly (lactic-co-glycolic acid)
PSMA: prostate-specific membrane antigen
RES: reticuloendothelial system
ROS: reactive oxygen species
TME: tumor microenvironment

Conflicts of Interest
The author declares that there are no conflicts of interest.

Ethics Approval and/or Participant Consent
Since the article is a literature review, ethics approval and participant consent were not required.

Authors' Contributions
US: made contributions to the conception and design of the study, conducted the literature search, extracted and analyzed the data, drafted the manuscript, revised and edited it critically for intellectual content, and gave final approval of the version to be published.

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