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Research Article

Nanotechnology-Based Drug Delivery Systems for Cancer Therapy: Targeting Mechanisms, Nanocarrier Platforms, Immunotherapy Integration, and Translational Challenges

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ABSTRACT

Conventional cytotoxic cancer therapies remain constrained by poor aqueous solubility, non-selective systemic biodistribution, dose-limiting organ toxicity, and acquired multidrug resistance. Similarly, although cancer immunotherapies have reshaped clinical oncology, their broader efficacy is curtailed by heterogeneous patient responses, poor solid-tumor infiltration, and systemic immune-related adverse events (irAEs). This structured narrative review synthesizes recent peer-reviewed literature (2024–2025) alongside foundational nanomedicine studies to evaluate nanotechnology-based drug delivery systems (nano-DDS) in oncology and examine why prolific preclinical innovation has yielded comparatively modest clinical translation. Drawing upon five recent primary review and editorial sources spanning general nano-DDS platforms, breast cancer, ovarian cancer, and cancer immunotherapy—supplemented by landmark mechanistic studies and two recent reviews on computational and artificial intelligence (AI)-guided nanocarrier design—this report compares lipid-based, polymeric, inorganic, and biomimetic nanocarriers across their physicochemical properties, targeting mechanisms, and stages of clinical maturity. Current clinical practice remains anchored by PEGylated liposomal and albumin-bound paclitaxel formulations, while experimental research increasingly converges with immune checkpoint blockade, non-viral in vivo chimeric antigen receptor (CAR) T-cell programming, and lipid nanoparticle (LNP)-mediated mRNA cancer vaccines. Across the reviewed literature, six persistent translational barriers emerge: marked inter- and intra-patient heterogeneity of the enhanced permeability and retention (EPR) effect in human tumors, plasma protein corona interference, tumor microenvironment heterogeneity, long-term toxicity and limited biodegradability of inorganic carriers, manufacturing and regulatory complexity, and the weak predictive validity of conventional murine xenograft models. Collectively, the evidence indicates that oncology nanoDDS have progressed

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from a passive-targeting concept to a clinically validated therapeutic modality, and that next-generation clinical advances will depend on AI-assisted corona and ligand optimization, biomimetic surface engineering, biomarker-stratified patient selection, and physiologically relevant human organoid and tumor-on-a-chip models.

INTRODUCTION

1.1 Background

Cancer remains one of the leading causes of morbidity and mortality worldwide, accounting for nearly 10 million deaths annually according to recent global epidemiological estimates [16]. Despite substantial advances in surgical resection, radiotherapy, cytotoxic chemotherapy, molecularly targeted therapy, and immunotherapy, the clinical management of both hematological and solid malignancies continues to be restricted by fundamental pharmacological and biological constraints. Conventional small-molecule chemotherapeutic agents frequently exhibit poor aqueous solubility, rapid systemic clearance, non-selective tissue biodistribution, and narrow therapeutic indices. Consequently, systemic administration exposes rapidly proliferating healthy tissues—such as bone marrow, gastrointestinal mucosa, and hair follicles—to off-target cytotoxicity, while subtherapeutic intratumoral drug concentrations foster multidrug resistance [17,18]. Biologic therapeutics, including monoclonal antibodies, immune checkpoint inhibitors (ICIs), adoptive cell therapies, and nucleic acid-based therapeutics, face distinct but equally significant hurdles, including enzymatic instability, restricted penetration across dense solid-tumor stroma, heterogeneous intratumoral distribution, variable patient response rates, and systemic immune-related adverse events (irAEs) [19,20]. In this review, emphasis is placed primarily on solid-tumor oncology.

Engineered at the nanometer scale (typically 1–1000 nm, with most clinical formulations operating between 10 and 200 nm), nanotechnology-based drug delivery systems (nano-DDS) offer a versatile platform to address these pharmacological limitations [3]. By encapsulating, conjugating, or electrostatic-complexing therapeutic payloads within tailored nanocarriers, nano-DDS can solubilize hydrophobic compounds, shield labile molecules from premature enzymatic degradation, prolong systemic circulation half-life, modulate release kinetics, and enable the co-delivery of synergistic drug combinations [3,9,17,18]. Clinical validation of oncology nanomedicine began with the regulatory approval of PEGylated liposomal doxorubicin (Doxil) in 1995 and nanoparticle albumin-bound paclitaxel (Abraxane) in 2005, followed by additional liposomal and polymeric formulations over the subsequent two decades [6,7,21,22]. More recently, the clinical deployment of lipid nanoparticle (LNP)-formulated mRNA vaccines during the COVID-19 pandemic demonstrated the scalability and clinical viability of nucleic acid nanocarriers at a global scale [15,23,24], accelerating the development of mRNA cancer vaccines and nanocarrier-enabled immunotherapies.

1.2 Research Gap and Rationale

Although numerous reviews have examined nano-DDS within individual disease contexts— such as breast cancer [1] or ovarian cancer [4]—or focused on specific formulation technologies [2,3], relatively few syntheses have integrated nanocarrier material chemistry, solid-tumor clinical trial landscapes, and the rapidly expanding interface between nanomedicine and cancer immunotherapy [5]. Furthermore, for nearly three decades, the rational design of oncology nanomedicines relied predominantly on passive tumor accumulation mediated by the enhanced permeability and retention (EPR) effect [26,27]. However, accumulating clinical and quantitative mechanistic evidence demonstrates that the EPR effect is highly heterogeneous across human patients and tumor subtypes due to variations in vascular perfusion, endothelial fenestration, extracellular matrix density, hypoxia, and elevated interstitial fluid pressure, whereas early preclinical benchmarks were largely established in rapidly growing murine xenograft models with exaggerated vascular permeability [10–12,25].

This discrepancy has contributed directly to the modest clinical translation rate of simple, passively targeted nanocarriers and has prompted a paradigm shift away from empirical trialand-error formulation toward three converging research directions: (i) computational and artificial intelligence (AI)-guided nanocarrier design, utilizing molecular docking, molecular dynamics (MD)

simulations, and machine learning (ML) models to predict nano–bio interactions and optimize ligand presentation prior to wet-lab synthesis [63,66,67]; (ii) plasma protein corona engineering, which treats adsorbed serum proteins as a programmable biointerface rather than merely an obstacle to circulation stability and target recognition [13,35]; and (iii) multi-stimuli-responsive and immunotherapy-integrated delivery platforms engineered to release chemotherapeutic payloads, immunomodulators, non-viral chimeric antigen receptor (CAR) constructs, or neoantigen mRNAs in response to tumor microenvironment (TME) triggers such as acidic pH, overexpressed matrix metalloproteinases, or elevated intracellular glutathione levels [5,14].

1.3 Objectives and Scope

The primary objectives of this review are sixfold: (1) to examine the biological foundations and in vivo physiological barriers governing nanocarrier performance, contrasting passive EPR-mediated accumulation with ligand-directed active targeting; (2) to classify and compare the major lipid-based, polymeric, inorganic, and biomimetic/cell-derived nanocarrier platforms with respect to their physicochemical attributes and clinical maturity; (3) to evaluate the emerging role of computational modeling and AI in rational nanocarrier optimization; (4) to analyze the convergence between nano-DDS and cancer immunotherapy modalities; (5) to synthesize disease-specific clinical and preclinical applications in breast and ovarian malignancies; and (6) to critically assess persistent translational barriers and outline actionable future research priorities.

The remainder of this report is organized as follows. Section 2 reviews the theoretical foundations of tumor targeting, protein corona dynamics, major nanocarrier classes, immunotherapy integration, and computational design strategies. Section 3 details the structured narrative review methodology, literature selection criteria, and thematic synthesis workflow. Section 4 presents the synthesized findings across carrier classes, breast and ovarian cancer applications, immunotherapy combinations, and cross-cutting translational barriers. Section 5 discusses the theoretical and practical implications of these findings, outlines the limitations of the review, and maps each barrier to emerging technological solutions. Section 6 summarizes the principal conclusions.

2. Literature Review

2.1 Theoretical Foundations: Passive and Active Targeting

Targeted delivery of nanomedicines to solid tumors relies on two complementary mechanistic strategies: passive targeting and active targeting [1,29,30]. Passive targeting exploits the pathophysiological features of the tumor vasculature—collectively termed the enhanced permeability and retention (EPR) effect—originally described by Matsumura and Maeda [26,27]. Whereas normal tissues possess tight endothelial junctions that retain macromolecules and nanoparticles within the vascular lumen, solid tumors undergoing rapid angiogenesis develop disorganized, fenestrated capillary endothelium accompanied by impaired lymphatic drainage. Nanoparticles engineered within an optimal hydrodynamic diameter window of approximately 10–200 nm and modified with hydrophilic stealth coatings such as polyethylene glycol (PEG) evade rapid renal filtration and reticuloendothelial clearance, achieving prolonged systemic circulation half-lives that permit gradual extravasation and retention within the tumor interstitium [6,12,28]. Nevertheless, quantitative analyses indicate that only a small fraction of injected nanoparticles typically reaches human solid tumors via passive diffusion alone, and that active trans-endothelial transport pathways frequently contribute to nanoparticle extravasation in vivo [10,11,25].

To overcome the limited cellular specificity of passive accumulation, active targeting strategies functionalize the nanocarrier surface with affinity ligands—including monoclonal antibodies, antibody fragments, peptides, aptamers, folate, transferrin, or hyaluronic acid—that selectively bind receptors overexpressed on malignant cells or tumor-associated vascular endothelium, such as human epidermal growth factor receptor 2 (HER2), folate receptor-alpha, transferrin receptor, or alpha-v beta-3 integrins [1,4,29,30]. While systemic biodistribution to the tumor bed remains governed primarily by vascular transport and extravasation, ligand–receptor engagement promotes selective retention

and receptor-mediated endocytosis, markedly increasing intracellular payload delivery once the carrier reaches the tumor microenvironment [29,30]. The mechanistic distinction between normal vascular retention, passive EPR extravasation, and ligand-mediated active targeting is illustrated in Figure 1.

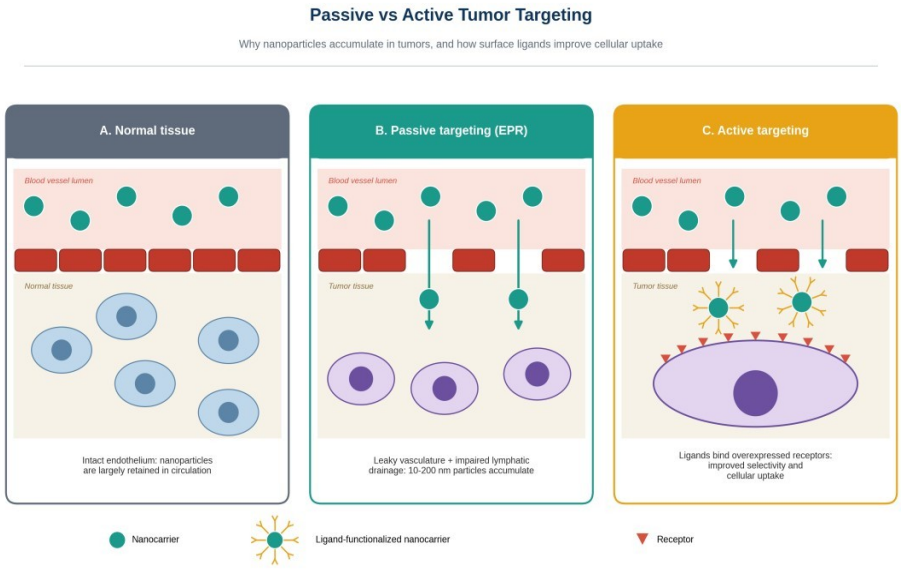

Figure 1: ***Schematic comparison of nanoparticle retention in normal tissue (A), passive EPR-mediated accumulation in tumor tissue (B), and ligand-functionalized active cellular targeting (C).***

2.2 The Protein Corona and Biological Barriers

Upon intravenous administration, nanoparticles immediately encounter complex physiological fluids and rapidly adsorb plasma proteins onto their surface, forming a dynamic biomolecular layer known as the 'protein corona' [1,13,31,32]. The composition and conformational state of this corona are governed by the nanoparticle's physicochemical properties—including hydrodynamic size, surface charge (zeta potential), hydrophobicity, and surface chemistry—as well as the local biological milieu [31,32,37]. Crucially, the protein corona establishes the effective 'biological identity' of the nanocarrier in vivo, dictating its pharmacokinetic profile, immune recognition, cellular uptake, and potential toxicity [31,34]. Enrichment of the corona with opsonins (such as immunoglobulins and complement proteins) promotes rapid recognition and clearance by macrophages of the mononuclear phagocyte system (MPS) in the liver and spleen, whereas preferential adsorption of dysopsonins (such as serum albumin and apolipoproteins) can extend systemic circulation time [1,33,34].

Beyond altering systemic clearance, an uncontrolled protein corona can sterically mask surface-conjugated targeting ligands—abolishing receptor-specific binding, as demonstrated for transferrin-functionalized nanoparticles—and impede controlled drug release kinetics [1,13,35]. In addition to corona formation and hepatic or renal filtration, systemically administered nanocarriers must traverse a sequential cascade of biological barriers: evasion of phagocytic clearance in circulation, extravasation across heterogeneous tumor vasculature, diffusive transport through dense extracellular stroma against elevated interstitial fluid pressure, cellular internalization across the plasma membrane, and timely endosomal escape prior to lysosomal acidification and enzymatic degradation of the therapeutic payload [9,18,36– 38]. This multi-stage in vivo journey and the principal barrier encountered at each step are summarized in Figure 2.

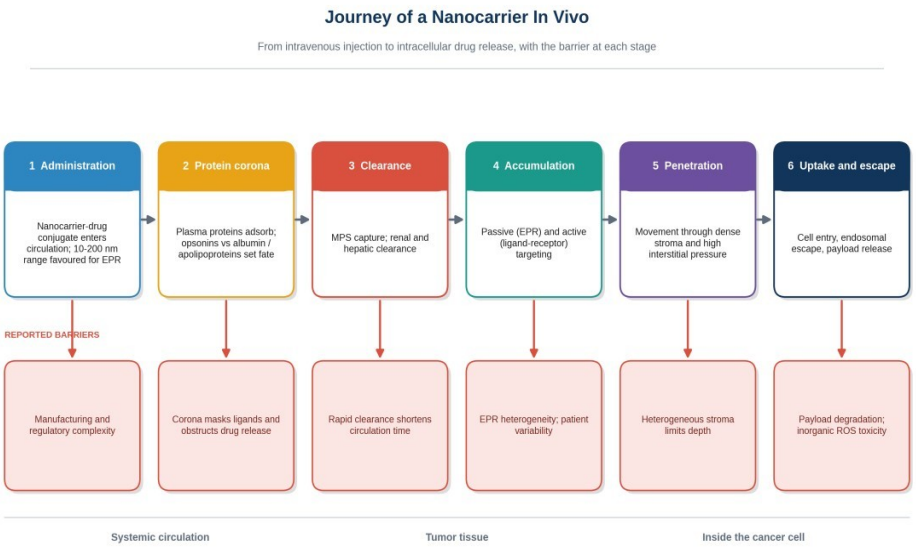

Figure 2: ***Sequential in vivo journey of a systemically administered nanocarrier from intravenous injection to intracellular payload release, highlighting the principal biological and translational barriers at each stage.***

2.3 Nanocarrier Classes Reported in Recent Literature

Recent oncology literature classifies drug delivery nanocarriers into four overarching structural categories: lipid-based, polymeric, inorganic, and biomimetic or cell-derived platforms [1,3,4]. Lipid-based nanocarriers—most notably PEGylated and non-PEGylated liposomes—represent the most clinically mature class, underpinned by approved oncology therapeutics including Doxil/Caelyx (PEGylated liposomal doxorubicin), Myocet (non-PEGylated liposomal doxorubicin), Onivyde (nanoliposomal irinotecan), Marqibo (liposomal vincristine), and Vyxeos (liposomal daunorubicin and cytarabine) [1,6,7,39–41]. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) offer enhanced physical stability and controlled release for lipophilic drugs [42], whereas ionizable lipid nanoparticles (LNPs) have emerged as the premier clinical vehicle for intracellular delivery of mRNA and small interfering RNA (siRNA) therapeutics [15,24]. Nevertheless, PEGylated lipid systems remain susceptible to anti-PEG antibody induction and the accelerated blood clearance (ABC) phenomenon upon repeated dosing [54,55].

Polymeric nanocarriers—encompassing biodegradable polymeric nanoparticles (such as poly (lactic-co-glycolic acid) [PLGA]), amphiphilic block copolymer micelles, and hyperbranched dendrimers—provide highly tunable degradation kinetics, efficient solubilization of hydrophobic taxanes and camptothecins (exemplified clinically by the polymeric micelle paclitaxel formulation Genexol-PM), and dense surface functional groups for multivalent ligand conjugation [1,3,4,43–45]. Inorganic nanocarriers, including gold nanoparticles, superparamagnetic iron oxide nanoparticles (SPIONs), mesoporous silica nanoparticles, semiconductor quantum dots, and carbon nanotubes, exhibit distinctive plasmonic, magnetic, and high-surface-area structural properties suited for diagnostic imaging, sentinel lymph node mapping, and photothermal or photodynamic therapy; however, concerns regarding heavy-metal persistence, limited long-term biodegradability, and reactive oxygen species (ROS)-mediated cytotoxicity continue to restrict their clinical approval [1,4,46–49]. Finally, biomimetic and cell-derived platforms—including extracellular vesicles (exosomes) and nanoparticles camouflaged with erythrocyte, leukocyte, platelet, or cancer-cell membranes—have gained prominence in 2024–2025 studies due to their low intrinsic immunogenicity, prolonged circulation, and homotypic tumor-homing capabilities [1,4,50– 53]. The structural taxonomy of these four carrier classes is depicted in Figure 3, and their comparative attributes are summarized in Table 1.

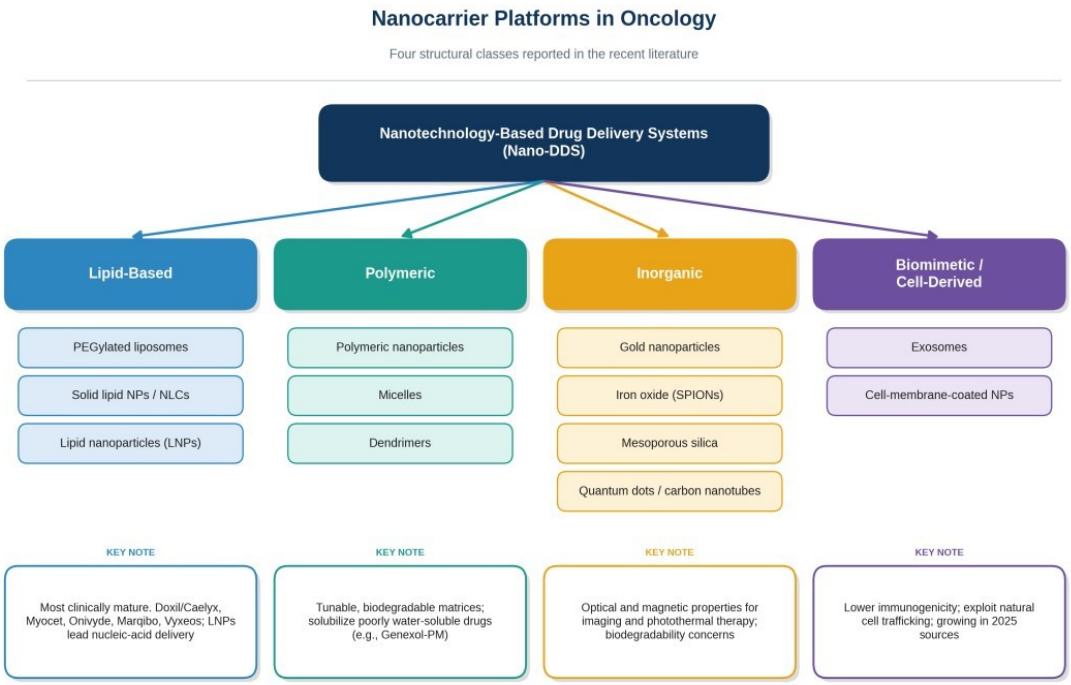

Figure 3: ***Structural classification of major nanocarrier platforms reported in the reviewed oncology literature.***

Table 1: Comparative Characteristics, Limitations, and Clinical Maturity of the Four Major Nanocarrier Classes Reported in the Reviewed Literature.

Carrier Class	Representative Platforms	Key Advantages	Principal Limitations / Concerns	Clinical Translation Status
Lipid-based	PEGylated and non-PEGylated liposomes; solid lipid nanoparticles (SLNs); nanostructured lipid carriers (NLCs); ionizable lipid nanoparticles (LNPs)	Most clinically mature class; high biocompatibility; improved physical stability (SLNs/NLCs); benchmark platform for nucleic acid delivery (LNPs) [1,6,7,15,24,42]	Opsonin-rich protein coronas can accelerate MPS clearance [1]; anti-PEG immunity and accelerated blood clearance (ABC) motivate PEG-free alternatives [54,55]	Multiple FDA/EMA-approved oncology products (Doxil/Caelyx, Myocet, Onivyde, Marqibo, Vyxeos) [1,6,7,39–41]; LNPs clinically validated in mRNA vaccines [15,23,24]
Polymeric	Biodegradable polymeric nanoparticles (e.g., PLGA); block copolymer micelles; dendrimers	Tunable molecular weight and release kinetics; efficient solubilization of hydrophobic drugs; multivalent surface ligand conjugation [1,3,4,43,44]	Architectural and chemical complexity complicates largescale GMP manufacturing and regulatory standardization [3,5,22]	Selected formulations in clinical use or late-estage trials (e.g., Genexol-PM polymeric micelle paclitaxel) [7,45]

Carrier Class	Representative Platforms	Key Advantages	Principal Limitations / Concerns	Clinical Translation Status
Inorganic	Gold nanoparticles; superparamagnetic iron oxide nanoparticles (SPIONs); mesoporous silica NPs; quantum dots; carbon nanotubes	Unique optical, plasmonic, magnetic, and porous properties enabling theranostics, MRI/sentinel node mapping, and photothermal therapy [1,4,46,47]	Incomplete biodegradation, long-term tissue retention, and reactive oxygen species (ROS)induced oxidative toxicity [1,48,49]	Predominantly preclinical or early-phase clinical trials (e.g., Phase I and Phase I/II diagnostic/therape utic trials in Table 2) [1,21]
Biomimetic / Cell-derived	Extracellular vesicles (exosomes); erythrocyte-, leukocyte-, or tumor cellmembrane-coated nanoparticles	Low immunogenicity; immune evasion; homotypic tumor recognition and natural biological trafficking [1,4,50–53]	Isolation heterogeneity, batch-to-batch variability, and complex scalable purification requirements [1,4,53]	Primarily preclinical and early Phase I clinical investigation, with rapid growth in 2024–2025 literature [1,4,52,53]

2.4 Convergence with Cancer Immunotherapy

A rapidly expanding body of oncology research focuses on integrating nano-DDS with cancer immunotherapy modalities, specifically immune checkpoint inhibitors (ICIs), chimeric antigen receptor (CAR) T-cell therapies, and personalized cancer vaccines [5,14,56–58]. Although ICIs targeting PD-1, PD-L1, and CTLA-4 have achieved durable clinical responses in subsets of patients, systemic antibody administration frequently triggers off-target autoimmune toxicities (irAEs) and suffers from limited penetration into immunologically 'cold' solid tumors [19,20,56]. Nanocarriers engineered for TME-responsive release can localize checkpoint blockade and immunomodulatory cytokines within the tumor bed and tumor-draining lymph nodes, enhancing antitumor T-cell priming while minimizing systemic immune hyperactivation [5,56,57]. Furthermore, synthetic lipid and polymeric nanocarriers are increasingly investigated as non-viral vectors capable of programming leukemia- or solidtumor-specific CAR T cells directly in situ, potentially bypassing the costly and labor-intensive ex vivo cell manufacturing required for conventional adoptive cell therapy [5,58,59]. Concurrently, ionizable LNP platforms validated during the COVID-19 pandemic are being adapted to protect and deliver tumor neoantigen-encoding mRNAs to antigen-presenting cells, eliciting poly-specific cytotoxic and helper T-cell responses in clinical and preclinical oncology settings [5,15,23,24,60].

2.5 Computational and AI-Guided Nanocarrier Design

To address the high attrition rate of empirical nanocarrier development, recent studies increasingly incorporate multiscale computational modeling and artificial intelligence into the formulation pipeline [63,66,67]. Atomistic and coarse-grained molecular dynamics (MD) simulations, coupled with molecular docking, enable quantitative prediction of drug–carrier binding energetics, lipid bilayer packing, surface ligand orientation, and receptor engagement prior to chemical synthesis [66,67]. In parallel, machine learning (ML) and deep learning algorithms trained on physicochemical and proteomic datasets are being deployed to predict plasma protein corona composition, optimize ligand density and stoichiometry, model drug release kinetics, and forecast in vivo biodistribution and tumor accumulation [63,66,67]. Integrating these in silico tools with experimental high-throughput screening shifts nanocarrier engineering from trial-and-error iteration toward rational, predictive design.

METHODOLOGY

3.1 Review Design

A structured narrative review methodology was adopted for this investigation. Given the rapid evolution of oncology nanomedicine and the pronounced methodological heterogeneity across preclinical physicochemical studies, animal tumor models, and early-phase clinical trials— which preclude uniform quantitative meta-analysis—a structured thematic synthesis provides the most rigorous framework for comparing carrier classes, mechanistic principles, and translational bottlenecks.

3.2 Literature Sources and Search Strategy

The primary evidence synthesis was anchored by five peer-reviewed articles published in 2024–2025: (1) a comprehensive review of nanotechnology-mediated precision drug delivery strategies for breast cancer published in Biomedicine & Pharmacotherapy [1]; (2) a review of nanoencapsulation technologies and transferable formulation principles for labile hydrophobic bioactives published in Molecules [2]; (3) a special-issue editorial synthesizing recent advances in nanotechnology-based drug delivery systems published in Pharmaceutics [3]; (4) a diseasefocused review of nano-DDS for the diagnosis and treatment of ovarian cancer published in Discover Oncology [4]; and (5) a review of emerging nanotechnology-driven drug delivery systems for cancer immunotherapy published in ACS Measurement Science Au [5]. To contextualize these recent findings within established nanomedicine theory, ten foundational articles addressing clinical translation, EPR heterogeneity, and protein corona dynamics were incorporated from the reference lists of the primary sources [6–15]. Additionally, authoritative background literature spanning cancer epidemiology, nanocarrier pharmacology, polymeric and biomimetic platforms, and organoid/microfluidic preclinical models [16–65], together with recent reviews on computational and AI-driven nanocarrier design [63,66,67], was integrated to support the mechanistic and discussion sections.

3.3 Selection Criteria

Literature sources were selected according to four predefined inclusion criteria: (a) direct relevance to nanomaterial- or nanocarrier-mediated drug delivery in oncology (or, in the case of source [2], transferable nanoencapsulation formulation mechanics for labile bioactive payloads); (b) publication in an indexed, peer-reviewed scientific journal; (c) inclusion of substantive preclinical, mechanistic, computational, or clinical trial evidence; and (d) publication within the 2024–2025 window for primary synthesis sources, supplemented by seminal earlier studies [6–65] for historical and mechanistic grounding. Non-English publications and unrefereed preprints were excluded.

3.4 Data Extraction and Thematic Synthesis

From each included source, structured information was extracted regarding nanocarrier material class and physicochemical composition, targeting mechanism (passive EPR versus ligand-mediated active targeting), malignancy or therapeutic modality investigated, key preclinical or clinical trial outcomes, and explicitly reported translational limitations. The extracted evidence was organized into five thematic domains—(1) nanocarrier platform distribution, (2) breast cancer clinical translation, (3) ovarian cancer delivery and theranostics, (4) cancer immunotherapy integration, and (5) cross-cutting biological and manufacturing barriers—to facilitate cross-source comparison in Section 4 and strategic mapping in Section 5. The overall review workflow is illustrated in Figure 4.

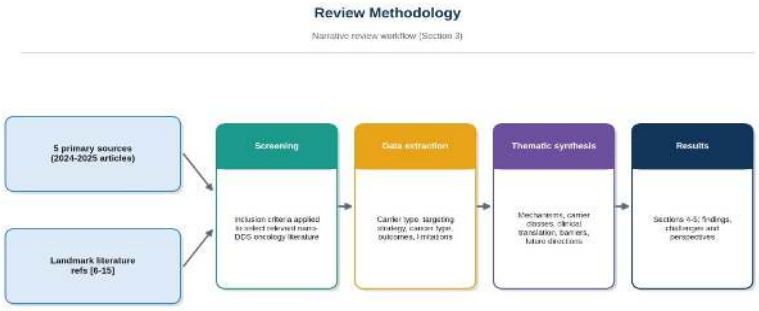

Figure 4: ***Structured narrative review workflow illustrating source selection, data extraction, and thematic synthesis.***

RESULTS

4.1 Distribution of Nanocarrier Classes Across the Reviewed Literature

Across the five primary 2024–2025 sources, lipid-based nanocarriers—particularly PEGylated and non-PEGylated liposomes and ionizable LNPs—were the most extensively documented platforms and accounted for the majority of clinically approved and late-stage oncology formulations [1,3,5]. Polymeric nanoparticles, polymeric micelles, and dendrimers constituted the second most frequently evaluated category, valued for their customizable degradation profiles and ability to encapsulate poorly water-soluble chemotherapeutics [1,3,4]. Inorganic nanomaterials (gold nanoparticles, SPIONs, mesoporous silica nanoparticles, quantum dots, and carbon nanotubes) ranked third, appearing primarily in diagnostic imaging, sentinel lymph node mapping, and photothermal or theranostic applications [1,4]. Biomimetic and cell-derived carriers, including exosomes and cell-membrane-camouflaged nanoparticles, represented a rapidly growing fourth category emphasized in the 2025 breast and ovarian cancer reviews as next-generation strategies to bypass immune clearance and improve homotypic tumor targeting [1,4].

4.2 Clinical Trial Landscape: Breast Cancer

Analysis of the breast cancer nanomedicine literature identified seven representative nanoparticle platforms evaluated across Phase I to Phase IV clinical trials, as compiled in Table 2 [1]. The distribution of these seven clinical-stage candidates by trial phase and carrier class is depicted in Figure 5. Notably, five of the seven clinical candidates utilize liposomal architectures (EndoTAG-1, DepoVax, PEGylated liposomal doxorubicin, mitoxantrone hydrochloride liposomes, and LIPUSU), whereas only two employ inorganic platforms (CdS/ZnS core–shell quantum dots in Phase I and SPION-based MagTrace in Phase I/II for sentinel lymph node biopsy) [1].

Table 2: Representative Nanoparticle Platforms in Clinical Development for Breast Cancer Reported in the Reviewed Literature [1].

Brand Name / Nanoplatform	Therapeutic or Diagnostic Agent	Oncology Indication	Clinical Phase	NCT Identifier
EndoTAG-1 (cationic liposomal paclitaxel)	Paclitaxel	Triple-negative breast cancer (TNBC)	Phase III	NCT03126435
DepoVax (liposomal peptide immunovaccine)	Tumor-associated antigens	Breast, ovarian, and prostate cancers	Phase I	NCT02472548

Brand Name / Nanoplatform	Therapeutic or Diagnostic Agent	Oncology Indication	Clinical Phase	NCT Identifier
QDs-VELD (CdS/ZnS core– shell quantum dots)	Veldoreotide (somatostatin analogue)	Breast cancer and skin cancer	Phase I	NCT04138342
MagTrace (SPIONs + Tc-99m tracer)	SPION magnetic tracer	Sentinel lymph node biopsy in breast cancer	Phase I/II	NCT05359783
PEGylated liposomal doxorubicin	Doxorubicin hydrochloride	Metastatic and HER2-positive breast cancer	Not specified	NCT05181202
Mitoxantrone hydrochloride liposomes	Mitoxantrone	Advanced solid neoplasms / breast cancer	Phase I	NCT02043756
LIPUSU (liposomal paclitaxel)	Paclitaxel	Advanced solid tumors / breast cancer	Phase IV	NCT01994031

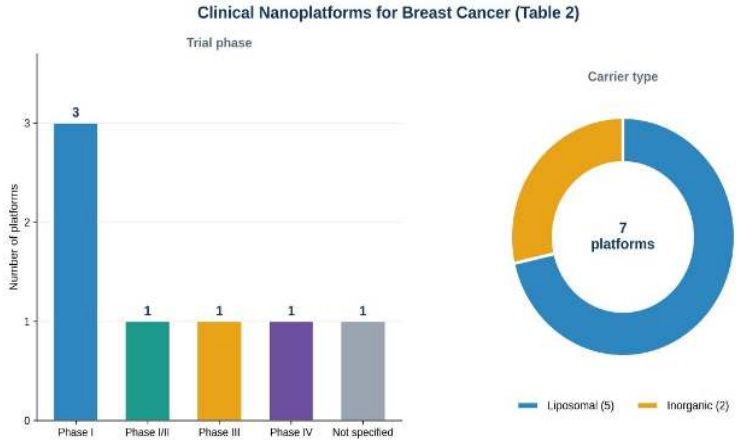

Figure 5: ***Distribution of the seven clinical-stage breast cancer nanoplatforms listed in Table 2 by clinical trial phase (left) and carrier class (right).***

Clinical outcome data synthesized in the breast cancer review further demonstrate the favorable safety and efficacy profiles of liposomal anthracyclines and taxanes [1]. In Phase III evaluation, PEGylated liposomal doxorubicin exhibited significantly lower hematological and nonhematological toxicity than capecitabine, with zero Grade 4 toxicities recorded, while combination therapy pairing liposomal doxorubicin with gemcitabine achieved a median overall survival of 16.1 months and a clinical benefit rate of 78% [1]. Similarly, dual HER2 blockade combined with non-PEGylated liposomal doxorubicin and paclitaxel induced high pathological complete response rates without treatment-related symptomatic cardiotoxicity [1].

4.3 Ovarian Cancer Applications

In the ovarian cancer literature, research centered on polymeric micelles, nanocapsules, PLGA nanoparticles, solid lipid nanoparticles, liposomes, and PAMAM dendrimers designed to overcome platinum and taxane resistance [4]. Because epithelial ovarian cancer frequently disseminates directly across the peritoneal cavity, intraperitoneal administration of sustainedrelease nanocarriers was highlighted as a strategic route to maximize local peritoneal tumor exposure while limiting systemic bone marrow and renal toxicity [4]. Additionally, because ovarian malignancies are predominantly diagnosed at advanced stages (FIGO Stage III/IV), strong emphasis was placed on multifunctional theranostic nanoplatforms that co-encapsulate imaging contrast agents (such as SPIONs, gold

nanostructures, or near-infrared fluorophores) alongside chemotherapeutic or gene-silencing payloads to enable simultaneous early detection, real-time biodistribution monitoring, and targeted therapy [4].

4.4 Integration with Cancer Immunotherapy

Synthesis of the immunotherapy-focused literature revealed that nano-DDS substantially enhance the therapeutic index of immunomodulatory agents by improving aqueous solubility, protecting biologic payloads from premature degradation, and localizing release within the tumor microenvironment to mitigate systemic irAEs [5,56]. Four principal integration strategies were identified across the reviewed sources: (1) TME-responsive nanocarriers for localized delivery of immune checkpoint inhibitors (anti-PD-1, anti-PD-L1, and anti-CTLA-4) and immunostimulatory adjuvants [5,56]; (2) synthetic lipid and polymeric nanoparticles serving as non-viral vectors for in situ programming of CAR T cells directly within the patient's circulation or lymphoid tissues [5,15,59]; (3) ionizable LNP formulations encapsulating personalized tumor neoantigen mRNAs to drive robust antigen presentation and cytotoxic Tlymphocyte activation [5,15,60]; and (4) synergistic photo-immunotherapy platforms, exemplified in preclinical triple-negative breast cancer (TNBC) models by a near-infrared (NIR)-responsive nanocarrier coupled with CRISPR-Cas9 knockdown of the granzyme B inhibitor SerpinB9, which restored CD8+ T-cell-mediated antitumor immunity [1]. These four convergent modalities are illustrated in Figure 6 and summarized in Table 3.

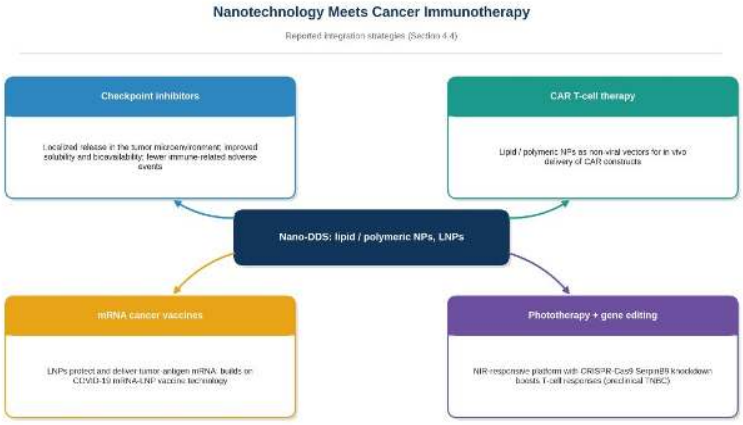

Figure 6: ***Four principal integration strategies combining nanotechnology-based drug delivery systems with cancer immunotherapy modalities.***

Table 3: Integration of Nanotechnology-Based Drug Delivery Systems with Cancer Immunotherapy Modalities in the Reviewed Literature.

Immunotherapy Modality	Functional Role of Nano-DDS	Reported Preclinical / Clinical Benefit and Status
Immune checkpoint inhibitors (ICIs)	Spatiotemporally controlled release within the tumor microenvironment; improved solubility and stability of smallmolecule and antibody immunomodulators	Enhanced intratumoral target engagement and T-cell infiltration; significant reduction in systemic immune-related adverse events (irAEs) [5,56,57]
CAR T-cell therapy	Synthetic lipid or polymeric nanoparticles engineered as nonviral vectors for targeted in vivo delivery of CAR-encoding nucleic acid constructs	Demonstrated in situ T-cell programming in preclinical models, offering a scalable alternative to ex vivo viral transduction [5,15,58,59]

Immunotherapy Modality	Functional Role of Nano-DDS	Reported Preclinical / Clinical Benefit and Status
mRNA cancer vaccines	Ionizable lipid nanoparticles (LNPs) protect tumor-antigen or neoantigen mRNA from ribonucleases and promote endosomal escape in dendritic cells	Potent poly-specific CD4+ and CD8+ T-cell responses; builds directly on clinically validated COVID-19 mRNA-LNP vaccine technology [5,15,23,24,60]
Phototherapy + CRISPR-Cas9 gene editing	Near-infrared (NIR)-responsive photothermal nanoplatform codelivering CRISPR-Cas9 ribonucleoprotein or plasmid targeting SerpinB9	Reversed tumor immunosuppressive resistance and amplified cytotoxic T-cell antitumor efficacy in preclinical TNBC models [1]

4.5 Reported Translational Barriers Across Sources

Cross-source synthesis revealed a consistent set of biological, toxicological, and industrial barriers that explain why only a small fraction of preclinical nanoformulations successfully advance to routine clinical oncology practice [1,3–5,10,21,22,61]. First, all mechanistic and clinical reviews emphasized the pronounced variability and unreliability of the passive EPR effect in human solid tumors compared with rapid-growth murine xenografts, resulting in heterogeneous intratumoral drug accumulation [1,10–12,25]. Second, rapid plasma protein corona adsorption was universally cited as a critical confounding factor that masks activetargeting ligands, alters surface charge, accelerates phagocytic clearance by the hepatic and splenic MPS, and disrupts programmed drug release profiles [1,13,31–35]. Third, substantial inter- and intra-patient tumor heterogeneity—including variable cell-surface receptor expression, dense desmoplastic stroma, hypoxia, and elevated interstitial fluid pressure — impedes uniform nanoparticle penetration throughout solid tumor masses [1,4,25].

Fourth, inorganic nanocarriers (such as quantum dots, carbon nanotubes, and nonbiodegradable metallic cores) face persistent safety hurdles related to poor physiological clearance, chronic tissue retention, and heavy-metal or ROS-induced organ toxicity [1,4,48,49]. Fifth, as nanocarriers incorporate multicomponent architectures—such as dual surface ligands, stimuli-responsive linkers, or biological membranes—they encounter severe bottlenecks in scalable Good Manufacturing Practice (GMP) synthesis, batch-to-batch reproducibility, physicochemical characterization, and regulatory approval [3,5,21,22,61]. Sixth, conventional subcutaneous murine xenograft models fail to recapitulate human tumor stromal architecture, vascular dynamics, and immune competency, creating a persistent preclinical-to-clinical translational gap [1,10,11,25,64,65].

DISCUSSION

5.1 Interpretation of Findings

The synthesized evidence demonstrates that oncology nano-DDS research is currently advancing along two distinct yet complementary trajectories. The first trajectory involves the clinical consolidation and iterative refinement of structurally simple, biocompatible lipid- and protein-based carriers—such as PEGylated and non-PEGylated liposomes and albumin-bound nanoparticles—which dominate approved clinical oncology products and late-stage breast cancer trials [1,6,7,21,62]. Their clinical success reflects primarily an improved safety and tolerability profile (such as reduced anthracycline cardiotoxicity and elimination of Cremophor EL solvent hypersensitivity) rather than dramatic increases in absolute tumor drug concentration [6,28,62]. The second trajectory comprises a rapid preclinical expansion into multifunctional biomimetic, inorganic, stimuli-responsive, and immunotherapy-integrated platforms that seek to overcome biological barriers actively, but remain predominantly in preclinical or early Phase I/II evaluation [1,4,5,7,8,22,61].

5.2 Comparison with Prior Literature

A defining shift observed in the 2024–2025 literature compared with foundational nanomedicine reviews from the 2000s and early 2010s is the critical reassessment of passive EPR targeting. Earlier paradigms

treated leaky tumor vasculature as a near-universal feature of solid malignancies that guaranteed preferential nanoparticle accumulation [6,8,26,27]. In contrast, contemporary studies explicitly integrate the quantitative findings of Wilhelm et al. [10], Sindhwani et al. [11], and Kang et al. [12], recognizing that human EPR permeability is highly variable and that active transendothelial transport, stromal modulation, and receptormediated endocytosis are essential for reliable intratumoral delivery. This theoretical evolution explains why recent 2025 reviews place heightened emphasis on active ligand functionalization, homotypic cell-membrane camouflaging, and localized intraperitoneal or intratumoral administration routes [1,4,5].

5.3 Practical and Theoretical Implications

From a practical pharmaceutical development perspective, the continued clinical predominance of liposomal and albumin-bound formulations underscores a vital translational lesson: formulation simplicity, excipient biocompatibility, and scalable GMP manufacturability are at least as decisive for regulatory approval and clinical adoption as sophisticated targeting chemistry [7,21,22,61,62]. Overly complex nanocarriers that cannot be reproduced consistently at industrial scale rarely survive clinical translation. From a theoretical perspective, the universal recognition of plasma protein corona interference across all reviewed sources implies that nanocarrier surface chemistry can no longer be optimized solely in buffer solutions; instead, dynamic corona formation in human plasma must be treated as an intrinsic, engineerable design parameter from the earliest stages of formulation development [1,13,31,34,35].

5.4 Limitations of This Review

Several methodological limitations should be considered when interpreting this report. First, because this study was conducted as a structured narrative review rather than a quantitative systematic review or meta-analysis, formal risk-of-bias scoring and pooled effect-size calculations were not performed. Second, the primary synthesis was anchored by five recent (2024–2025) peer-reviewed articles [1–5] and English-language literature; although supplemented by 60 foundational and mechanistic studies [6–65], this scope may not capture every emerging nanoplatform across all solid and hematological malignancies. Third, one primary source [2] examined nanoencapsulation principles for labile essential-oil bioactives rather than oncology therapeutics directly, and was utilized solely for generalizable formulation stability insights. Fourth, because a substantial proportion of the biomimetic, inorganic, and gene-editing nanoplatforms reported in recent literature remains at the preclinical stage, their long-term clinical safety and efficacy in human trials remain to be established. Finally, the discussion of computational and AI-guided nanocarrier design in Section 2.5 relies on secondary review literature [63,66,67].

5.5 Future Directions

Addressing the six translational barriers identified in Section 4.5 requires a coordinated shift toward six corresponding research priorities: (1) replacing passive EPR reliance with rational active targeting and biomimetic or cell-membrane-camouflaged carriers that exploit natural cellular trafficking [1,4,50–53]; (2) deploying AI, machine learning, and molecular dynamics simulations (Section 2.5) to predict plasma protein corona profiles, optimize ligand orientation, and design corona-resistant or corona-directed surfaces [13,35,63,66,67]; (3) implementing biomarker-guided patient stratification—including companion diagnostic imaging using radiolabeled or magnetic nanoparticles—to pre-select patients whose tumors exhibit sufficient vascular permeability or target receptor expression [1,61]; (4) prioritizing biodegradable, biocompatible, and environmentally sustainable carrier materials to eliminate chronic inorganic tissue accumulation and ROS toxicity [1,48,49]; (5) streamlining formulation architectures to favor scalable, reproducible GMP manufacturing and harmonized regulatory evaluation [3,5,22,61]; and (6) replacing conventional murine xenografts with physiologically predictive human preclinical models, including patient-derived tumor organoids and microfluidic vascularized tumor-on-a-chip systems [64,65]. The direct alignment between each persistent translational barrier and its corresponding future research direction is illustrated in Figure 7 and detailed in Table 4.

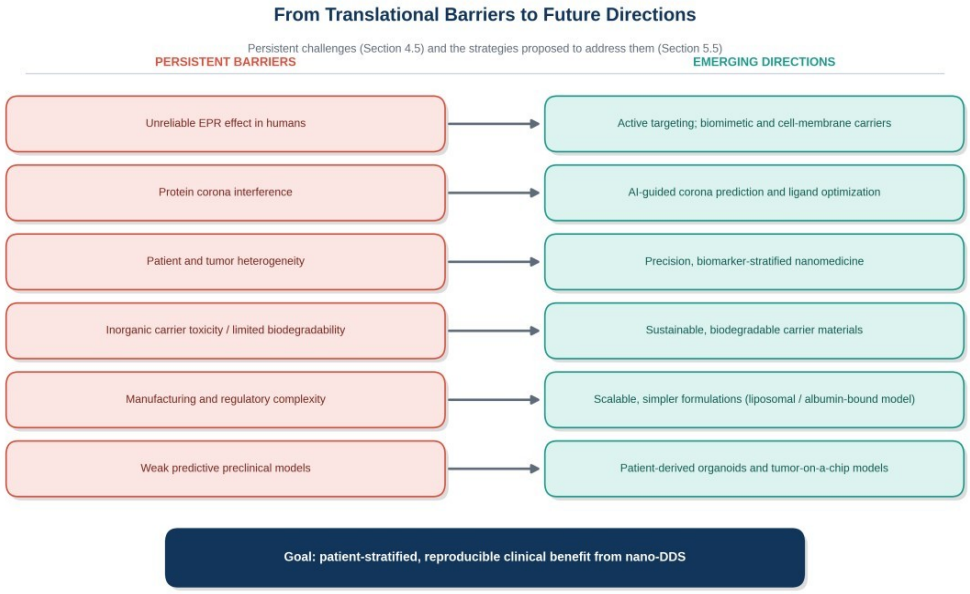

Figure 7: ***Strategic mapping of the six persistent translational barriers identified in Section 4.5 to emerging technological directions discussed in Section 5.5.***

Table 4: Summary of Reported Translational Barriers, Clinical Consequences, and Corresponding Future Research Directions.

Reported Translational Barrier	Clinical / Pharmacological Consequence	Proposed Future Strategy	Corresponding Report Sections
Unreliable and heterogeneous EPR effect in human solid tumors	Formulations with high efficacy in murine xenografts fail to achieve comparable intratumoral accumulation or survival benefit in Phase II/III clinical trials [10–12,25]	Ligand-directed active targeting; homotypic biomimetic and cellmembrane-coated nanocarriers; localized delivery routes [1,4,29,30,50–53]	Sections 2.1, 4.5, 5.2, 5.5
Plasma protein corona adsorption and interference	Masking of surface targeting ligands; altered zeta potential; accelerated hepatic/ splenic MPS clearance; impeded payload release [1,13,31–35]	AI/ML-guided protein corona prediction and ligand density optimization; engineering dysopsonin-recruiting biomimetic surfaces [13,35,63,66,67]	Sections 2.2, 2.5, 4.5, 5.3, 5.5
Inter- and intrapatient tumor microenvironment heterogeneity	Highly variable nanoparticle extravasation, stromal penetration depth, and receptor-mediated cellular uptake across patients [1,4,25]	Precision, biomarkerstratified nanomedicine utilizing companion diagnostic imaging (e.g., SPION/radionuclide theranostics) to preselect responders [1,4,61]	Sections 4.2, 4.3, 4.5, 5.5

Reported Translational Barrier	Clinical / Pharmacological Consequence	Proposed Future Strategy	Corresponding Report Sections
Inorganic carrier toxicity and poor longterm biodegradability	Chronic heavy-metal or nanoparticle accumulation in reticuloendothelial organs; reactive oxygen species (ROS)-mediated cellular toxicity [1,4,48,49]	Development of fully biodegradable, metabolizable organic/hybrid matrices and green-chemistry synthesis protocols [1,3,4,48,49]	Sections 2.3, 4.5, 5.5
Manufacturing scaleup and regulatory complexity	Multi-component, surface-functionalized, or cell-derived nanoformulations face severe batch-to-batch variability and GMP scale-up bottlenecks [3,5,21,22,61]	Prioritize streamlined, modular, and scalable architectures modeled on clinically proven liposomal, LNP, and albumin-bound platforms [6,7,21,22,61,62]	Sections 2.3, 4.5, 5.1, 5.3, 5.5
Reported Translational Barrier	**Clinical / Pharmacological Consequence**	**Proposed Future Strategy**	**Corresponding Report Sections**
Weak predictive validity of conventional murine preclinical models	High clinical trial attrition due to mismatch between murine xenograft vascular/ stromal biology and human solid tumors [10,11,25]	Integration of patientderived 3D tumor organoids and microfluidic human tumor-on-a-chip platforms into preclinical screening [64,65]	Sections 1.2, 4.5, 5.5

CONCLUSION

This structured narrative review synthesized recent (2024–2025) and foundational scientific literature on nanotechnology-based drug delivery systems in oncology to examine the persistent gap between prolific preclinical nanocarrier innovation and clinical translation. Three overarching conclusions emerge from this analysis. First, oncology nano-DDS have matured from theoretical constructs into a clinically validated therapeutic modality, anchored by approved liposomal, polymeric micelle, and albumin-bound formulations that significantly improve the safety and pharmacokinetic profiles of cytotoxic chemotherapeutics in breast, ovarian, and other solid malignancies. Second, the clinical translation of next-generation nanocarriers remains constrained by well-defined biological and industrial bottlenecks—most notably the heterogeneity of the human EPR effect, plasma protein corona interference, dense tumor stroma, inorganic carrier persistence, and GMP manufacturing complexity. Third, the convergence of nanotechnology with cancer immunotherapy—spanning localized checkpoint blockade, non-viral in situ CAR T-cell programming, and LNP-delivered mRNA cancer vaccines—represents the most dynamic frontier in contemporary nanomedicine. Overcoming current translational barriers will require integrating AI-guided computational design, biomimetic surface engineering, biomarker-driven patient stratification, and physiologically predictive human organoid and tumor-on-a-chip models to achieve reproducible, patientstratified clinical benefit.

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