

Nanoparticle-Based Targeted Drug Delivery Systems for Precision Cancer Therapy

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Abstract

Cancer remains one of the leading causes of mortality worldwide, largely due to limitations in conventional chemotherapy such as non-specific toxicity, poor drug solubility, and systemic side effects. Nanoparticle-based targeted drug delivery systems have emerged as a promising strategy to overcome these challenges by enabling precision cancer therapy. This study paper examines recent advances in the design, functionalization, and application of nanoparticles for targeted drug delivery in oncology. Various nanoparticle platforms, including liposomes, polymeric nanoparticles, dendrimers, metallic nanoparticles, and lipid-based nanocarriers, are discussed in terms of their physicochemical properties and therapeutic potential. The review highlights targeting strategies such as passive targeting through the enhanced permeability and retention (EPR) effect and active targeting using ligand-receptor interactions to improve tumor specificity. Additionally, the

role of nanoparticles in controlled drug release, multi-drug delivery, and combined therapeutic modalities such as chemotherapy, photothermal therapy, and gene therapy is explored. Despite significant progress, challenges including toxicity concerns, immune clearance, large-scale manufacturing, and clinical translation remain critical barriers. This review synthesizes current knowledge on nanoparticle-mediated drug delivery and emphasizes its potential to revolutionize precision cancer therapy by improving therapeutic efficacy while minimizing adverse effects.

Introduction

The therapeutic paradigm for oncological malignancies is undergoing a fundamental shift from systemic, non-specific cytotoxic intervention toward a model

defined by molecular precision and patient-specific calibration (Hong et al., 2023). Traditional chemotherapy, while efficacious in many contexts, is perpetually constrained by a narrow therapeutic index, where the dosage required for tumor eradication often approaches levels that induce prohibitive systemic toxicity. This clinical bottleneck is further exacerbated by the inherent heterogeneity of the tumor microenvironment (TME) and the rapid emergence of multidrug resistance (MDR) mechanisms that render initial treatment regimens ineffective over time (Yao et al., 2020). To address these systemic failures, nanotechnology has emerged as a transformative engine for drug delivery, offering engineered platforms capable of navigating the complex biological barriers of the human body to deliver therapeutic payloads directly to malignant cells with sub-cellular accuracy (Hasan et al., 2024).

As of the 2024–2025 period, the field has progressed beyond simple encapsulation toward “smart” nanomedicines that integrate active targeting, stimuli-responsive release, and real-time diagnostic monitoring (Li et al., 2022). These nanoparticle-based drug delivery systems (NDDS) leverage the unique physicochemical properties of materials at the nanoscale typically defined between 1 nanometer and 1000 nanometers to modulate the pharmacokinetics and biodistribution of potent chemotherapeutics, nucleic acids, and immunomodulatory agents (Dang & Guan, 2020). This comprehensive review delineates the current state of nanomedicine, analyzing the mechanisms of targeting, the diversity of delivery platforms, the critical role of the protein corona, and the integration of artificial intelligence in optimizing these sophisticated systems for clinical translation (Yang et al., 2021).

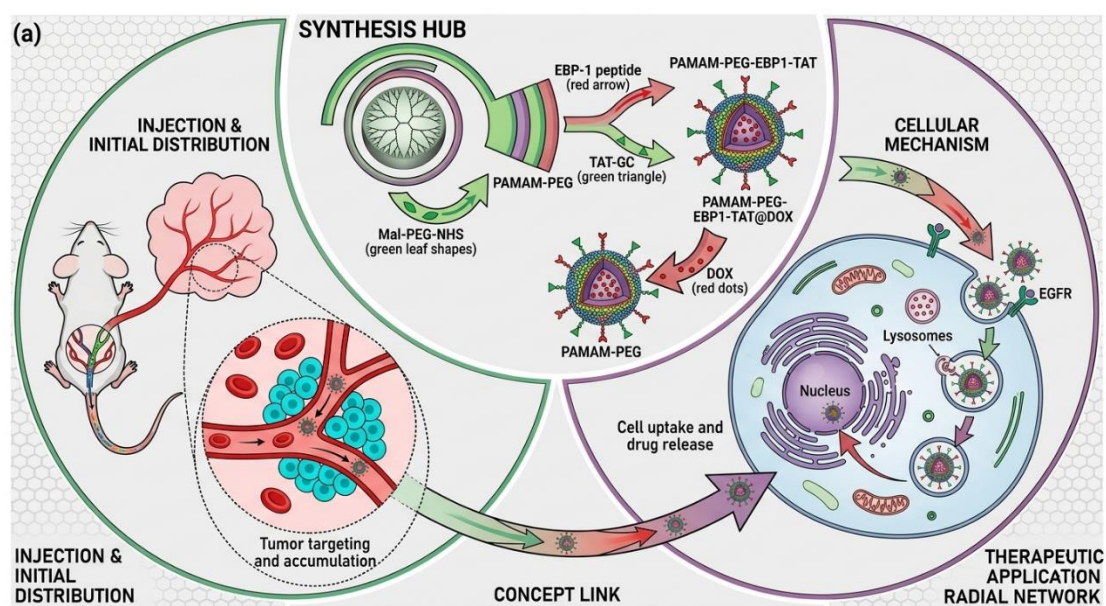
Mechanistic Evolution of Tumor Accumulation: The Passive and Active Targeting Continuum

The localization of nanoparticles within malignant tissue is governed by a continuum of targeting strategies, beginning with the foundational principle of passive accumulation and advancing toward highly specific, ligand-mediated interactions (Chen et al., 2020).

The Enhanced Permeability and Retention Effect: Current Status and Re-evaluation

The Enhanced Permeability and Retention (EPR) effect has long served as the guiding principle for cancer nanomedicine development. This phenomenon is rooted in the pathological angiogenesis characteristic of solid tumors, where the rapid proliferation of cancer cells demands an expanded vascular network (Manzari-Tavakoli et al., 2024). This neovasculature is structurally and functionally impaired, exhibiting disordered architecture, incomplete basement membranes, and large endothelial fenestrations that range in size from 100 nanometers to 600 nanometers (Hristova-Panusheva et al., 2024). These vascular “leaks” allow nanoparticles to extravasate from the bloodstream into the interstitial space of the tumor more readily than into healthy tissues. Furthermore, the compromised lymphatic drainage within the tumor core prevents the clearance of these extravasated materials, leading to their prolonged retention and a several-fold increase in local drug concentration (Emeihe et al., 2024).

Figure 1. In Vivo Accumulation Cascade and Subcellular Drug Release Processing of EGFR-Targeted Polymeric Nanocarriers Post-Injection



Despite its foundational role, the clinical utility of the EPR effect has been the subject of intense debate in the 2024–2025 literature. Evidence suggests that while EPR is a robust driver of accumulation in murine xenograft models, its manifestation in human patients is highly heterogeneous. Variability in tumor type, stage, location, and the degree of interstitial fluid pressure (IFP) can significantly impede passive delivery (Al Bostami et al., 2022). Elevated IFP, caused by high cell density and a rigid extracellular matrix, creates a pressure gradient that counteracts the convective forces necessary for nanoparticle extravasation, often confining nanomedicines to the tumor periphery. Consequently, contemporary research is shifting toward strategies that enhance or "prime" the EPR effect through vascular normalization, enzymatic degradation of the stroma, or physical triggers such as ultrasound-mediated cavitation (Yang et al., 2022).

Active Targeting via Ligand-Receptor Recognition

To move beyond the limitations of passive accumulation, active targeting utilizes the functionalization of nanoparticle surfaces with ligands that exhibit high affinity for receptors overexpressed on cancer cells or the tumor-associated endothelium (Onugwu et al., 2023). This approach is not merely designed to increase the total amount of nanoparticle accumulation but to facilitate receptor-mediated endocytosis, ensuring that the therapeutic payload is internalized directly into the cytoplasm or nucleus of the target cell (Lohiya & Katti, 2022).

The repertoire of targeting moieties has expanded considerably. Peptides, particularly the Arg-Gly-Asp (RGD) motif, remain prominent due to their ability to bind alpha-v beta-3 integrins, which are ubiquitous in both malignant cells and angiogenic vasculature (Mumtaz et al., 2021). Research highlights that cyclic RGD (cRGD) structures provide superior stability and binding affinity compared to linear variants, as exemplified by the clinical progression of cRGD-modified platforms (Thakuria et al., 2021).

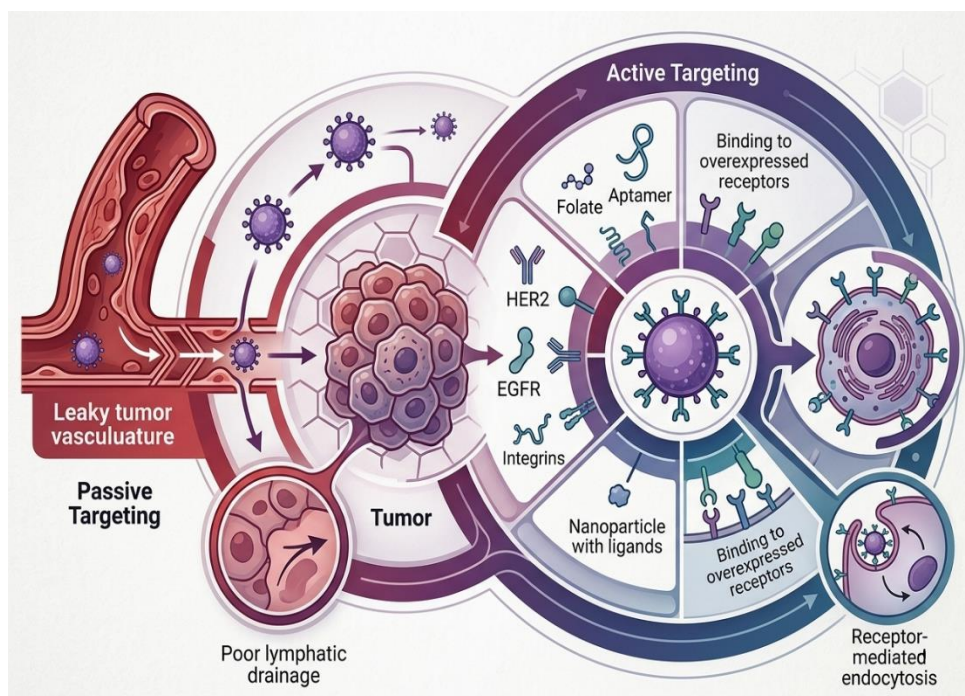
Beyond peptides, the use of nanobodies (Nbs) single-domain antibodies derived from camelids has gained traction due to their small size, high solubility, and ability to access hidden epitopes that are sterically hindered for conventional antibodies (Sv et al., 2024).

Table. 1. Targeting Moieties for Active Nanoparticle-Mediated Cancer Therapy: Receptors, Applications, and Mechanisms

Targeting Moiety	Target Receptor	Primary Clinical Application	Mechanistic Insight
cyclic RGD peptides (cRGD)	$\alpha v\beta 3$ integrin	Glioblastoma, gastric cancer	Targets neovasculature and invasive tumor cells
Nanobodies (single-domain antibodies)	HER2, EGFR, PSMA	Breast and prostate cancer	Small size enables deeper tissue penetration
Folic acid	Folate receptor alpha	Ovarian and lung cancer	Exploits high-affinity vitamin uptake pathways
Transferrin	Transferrin receptor	Solid tumors, blood-brain barrier crossing	Utilizes iron transport machinery overexpressed in cancer
Aptamers	PD-L1, PSMA	Triple-negative breast cancer	DNA/RNA ligands that mimic antibody specificity
Hyaluronic acid	CD44 receptor	Cancer stem cells	Targets highly metastatic and stem-like tumor cell populations

The clinical significance of active targeting is underscored by the development of platforms like 2B3-101, which leverages a glutathione (GSH) tripeptide for the delivery of chemotherapy across the blood-brain barrier (BBB) to treat cerebral metastases (Nkune & Abrahamse, 2021). In Phase I/IIa trials involving patients with breast cancer-related brain metastases, this approach demonstrated a 56% progression-free survival rate at 12 weeks, validating the potential for ligand-mediated delivery to overcome the most restrictive biological barriers (Xie et al., 2021).

Figure 2: Physiological Barriers and Receptor-Mediated Pathways in Nanomedicine Cancer Targeting.



Structural Classification and Physicochemical Customization of Nanocarriers

The selection of a nanocarrier platform is determined by the required drug loading capacity, the solubility of the therapeutic agent, and the desired release kinetics. Nanoparticles are broadly classified into organic, inorganic, and hybrid systems, each offering unique advantages for precision therapy (Wu et al., 2022).

Organic Platforms: Biocompatibility and Clinical Maturity

Organic nanoparticles, including liposomes, polymeric nanoparticles, and dendrimers, represent the most clinically successful class of NDDS. Liposomes, characterized by their phospholipid bilayer structure, are particularly versatile as they can encapsulate hydrophilic drugs in their aqueous core and hydrophobic drugs within the lipid membrane (Stefanache et al., 2025). To address the challenge of rapid clearance by the mononuclear phagocyte system (MPS), "stealth" liposomes are functionalized with polyethylene glycol (PEG), which creates a steric barrier that inhibits opsonization (Chouaib et al., 2020).

Polymeric nanoparticles provide a more rigid alternative, often utilizing biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA) or polyethyleneimine (PEI). These systems can be engineered as nanospheres where the drug is dispersed within a polymer matrix or nanocapsules where a drug core is surrounded by a polymer shell allowing for precisely tuned sustained-release profiles (Herdiana, 2025). Dendrimers, as monodisperse, highly branched macromolecules, allow for the attachment of multiple drugs and targeting ligands on their surface, creating a high-valency system capable of overcoming weak individual receptor-ligand interactions (Reddy & Reddy, 2025).

Inorganic and Hybrid Systems: Multifunctionality and Stability

Inorganic nanoparticles, such as those based on gold, silica, and magnetic iron oxide, offer physical properties that organic carriers lack. Gold nanoparticles are extensively utilized in photothermal therapy (PTT) due to their surface plasmon resonance, while magnetic nanoparticles enable both magnetic resonance imaging (MRI) and thermal ablation under an alternating magnetic field (Qu et al., 2024). Mesoporous silica nanoparticles (MSNs) are valued for their exceptional surface area and tunable pore structures, which facilitate exceptionally high drug loading and the integration of stimuli-responsive "gatekeepers" to control release (Fatima et al., 2022).

Polymer-lipid hybrid nanoparticles (PLHNPs) represent a convergence of these technologies, integrating a polymeric core for high drug retention with a biomimetic

lipid shell for enhanced biocompatibility (Sarvari & Sarvari, 2023). The structure typically comprises three elements: a hydrophobic polymer core, a lipid monolayer interface, and an outer PEGylated lipid bilayer. This architecture has demonstrated superior performance in maintaining drug stability and achieving prolonged circulation compared to traditional liposomal or polymeric systems alone (Kordkatouli et al., 2024).

Biomimetic Nanotechnology: Harnessing "Self" Signatures

One of the most profound innovations in the 2024–2025 period is the rise of biomimetic nanocarriers, specifically cell membrane-coated nanoparticles. By encasing synthetic nanoparticle cores in natural membranes derived from red blood cells (RBCs), platelets, or macrophages, researchers can camouflage the delivery system from the immune system (Pramanik, et al., 2021). RBC membrane-coated particles, for example, express surface markers such as CD47 (the "don't eat me" signal), allowing them to circulate for up to 40 hours in murine models significantly outperforming conventional PEGylated nanoparticles. Platelet membrane coatings further enhance targeting to tumor vasculature and sites of inflammation, leveraging the natural homing capabilities of these cells (Yan et al., 2020).

Exosomes, a subset of extracellular vesicles, are also being explored as natural delivery vehicles. These vesicles are inherently designed for intercellular communication and can protect sensitive cargoes, such as mRNA or siRNA, from RNase-mediated degradation in the systemic circulation. Their low immunogenicity and natural tropism for specific tissues make them ideal for next-generation personalized nanomedicine (Kumar et al., 2026).

Biological Barriers and the "Biological Identity" of Nanoparticles

The transition of nanoparticles from an engineered state to a biological environment results in the formation of the protein corona (PC), a process that fundamentally alters the nanoparticle's fate and targeting efficiency (Mittal et al., 2025).

The Protein Corona: Composition and Impact

The protein corona is a dynamic layer of biomolecules that spontaneously adsorb onto the nanoparticle surface upon contact with blood, plasma, or interstitial fluid. This corona provides the nanoparticle with its "biological identity," which is what the cellular machinery actually recognizes, rather than the intended engineered surface. The PC composition is governed by the nanoparticle's size, shape, surface charge (zeta potential), and material composition (Park et al., 2025).

The impact of the protein corona (PC) is dual in nature. Opsonins, such as immunoglobulins and complement proteins (for example, C3), mark nanoparticles for rapid phagocytosis by the macrophages of the liver (Kupffer cells) and spleen, leading to systemic clearance (Yu et al., 2020). Conversely, the adsorption of dysopsonins, such as clusterin (ApoJ) or specific apolipoproteins (ApoE), can impart "stealth" properties or facilitate receptor-mediated crossing of the blood–brain barrier (BBB). For instance, the selective recruitment of ApoE and ApoB-100 onto silica- or lipid-based nanoparticles smaller than 100 nanometers has been linked to enhanced delivery efficiency to the brain (Gu & Minko, 2024).

Table 2. Key Protein Corona Components and Their Influence on Nanoparticle Biodistribution and Therapeutic Performance

Corona Protein	Predominant Nanoparticle Substrate	Biological Outcome	Clinical Significance
Apolipoprotein E (ApoE) / Apolipoprotein B-100 (ApoB-100)	Silica, lipid-based nanoparticles (less than 100 nm)	Receptor-mediated cellular uptake	Improved brain and liver targeting

	nanometers)		
Complement C3	Metal and metal-oxide nanoparticles (greater than 100 nanometers, negatively charged zeta potential)	Immune recognition by the mononuclear phagocyte system (MPS)	Rapid systemic clearance; potential toxicity
Clusterin (ApoJ)	PEGylated or neutrally charged surfaces	Dysopsonization (reduction of immune recognition)	Prolonged blood circulation time
Albumin	Hydrophobic polymer-based nanoparticles	Caveolae-mediated endocytosis	Targeted delivery to lung and tumor tissues

Overcoming the Mononuclear Phagocyte System and Tissue Sequestration

The liver is the primary site of nanoparticle sequestration, with Kupffer cells eliminating the vast majority of systemically administered nanomedicines. This sequestration acts as a major bottleneck for achieving tissue-specific delivery (Manzari et al., 2021). Strategies to overcome this include "pre-conditioning" the liver or engineering nanoparticles that avoid the adsorption of opsonins through surface modifications like PEGylation or biomimetic coatings. However, the "PEG dilemma" the observation that repeated doses can trigger anti-PEG antibodies and lead to accelerated blood clearance remains a significant hurdle in long-term treatment protocols (Das, 2023).

Stimuli-Responsive Release: Achieving Spatiotemporal Precision

The efficacy of precision cancer therapy is fundamentally tied to the ability of the nanocarrier to remain stable in the systemic circulation but release its cargo rapidly upon arrival at the tumor site. This is achieved through the development of stimuli-responsive "smart" nanoparticles that respond to either endogenous TME cues or exogenous physical triggers (Cheng et al., 2023).

Endogenous Triggers: Exploiting the Pathological Microenvironment

The TME is characterized by unique chemical and biological gradients that distinguish it from normal physiological conditions:

1. **pH-Responsive Systems:** Solid tumors exhibit an acidic extracellular environment (pH approximately 6.5–6.8) due to increased glycolysis, known as the Warburg effect. Intracellular compartments such as endosomes (pH approximately 5.5) and lysosomes (pH approximately 4.5–5.0) are even more acidic. Nanoparticles engineered with acid-labile bonds (for example, hydrazones and orthoesters) or pH-sensitive polymers can undergo conformational changes or degradation to release drugs specifically within these compartments (Zhang et al., 2023).
2. **Redox-Responsiveness:** The intracellular concentration of glutathione (GSH) in cancer cells is significantly higher (2–10 millimolar) than in the extracellular space (2–20 micromolar). Nanocarriers containing disulfide, ditelluride, or thioether bonds can be rapidly cleaved by GSH, facilitating the "burst" release of therapeutics particularly genetic material once internalized (Bajpai et al., 2021).
3. **Enzymatic Activation:** Overexpressed enzymes in the TME, such as matrix metalloproteinases (MMPs), cathepsins, and phospholipases, can be used as biological triggers. Peptide-based linkers designed for specific enzymatic cleavage ensure that the drug is liberated only in the presence of tumor-specific proteolytic activity (Yao et al., 2025).

4. **Hypoxia-Triggered Release:** Hypoxia is a hallmark of aggressive tumors. Nanoparticles utilizing hypoxia-sensitive moieties, such as azobenzene or nitroimidazole, can release their cargo in the oxygen-deprived core of solid tumors, where traditional therapies often fail (Mohtar et al., 2021).

Exogenous Triggers: Remote Control of Drug Action

Exogenous stimuli provide clinicians with the ability to trigger release with high spatial and temporal resolution using external devices:

- **Light-Triggered Release:** Near-infrared (NIR) light is preferred for its deeper tissue penetration and minimal absorption by water and hemoglobin. NIR can activate photosensitizers within nanoparticles to generate reactive oxygen species (ROS) or induce localized heating in thermosensitive liposomes (LTSLs), as demonstrated in studies combining high-intensity focused ultrasound (HIFU) with doxorubicin-loaded LTSLs (Qin et al., 2023).
- **Magnetic Field-Controlled Release:** Magnetic nanoparticles subjected to alternating magnetic fields can generate localized heat (hyperthermia), triggering release from heat-sensitive matrices or inducing direct thermal damage to tumor cells (Kapoor et al., 2024).
- **Ultrasound and Cavitation:** Ultrasound can be used to induce the transient formation of pores in the tumor vasculature and cell membranes, enhancing the penetration and uptake of nanoparticles a process critical for treating poorly perfused tumor regions (Chen et al., 2023).

Nanotechnology and the Reversal of Multidrug Resistance

Drug resistance, often mediated by the overexpression of ATP-binding cassette (ABC) transporters such as P-glycoprotein (P-gp), is a primary cause of chemotherapy failure in metastatic disease. These efflux pumps actively transport drug molecules out of the cell before they can reach their intracellular targets (Ajith et al., 2023).

Nanoparticle-based delivery systems circumvent these mechanisms by altering the route of cellular entry. By entering cells through endocytic pathways, nanoparticles bypass plasma membrane-bound P-glycoprotein (P-gp) pumps, effectively delivering the drug cargo into endosomes and lysosomes. Furthermore, nanotechnology enables the co-delivery of chemotherapeutic agents and resistance-modulating compounds (for example, P-gp inhibitors) within a single carrier (Rajendran et al., 2024).

For example, studies using PLGA nanoparticles to co-deliver doxorubicin and the inhibitor tariquidar have shown a 7.3-fold reduction in IC₅₀ values in resistant breast cancer lines, effectively restoring drug sensitivity to levels seen in parental non-resistant lines. Other innovative approaches include the use of siRNA-loaded nanoparticles to silence the expression of genes involved in multidrug resistance or anti-apoptotic pathways such as Bcl-2 and HIF-1 alpha (Tiwari et al., 2023).

Artificial Intelligence and Machine Learning in NDDS Optimization

The development of high-performance nanocarriers is increasingly reliant on artificial intelligence (AI) and machine learning (ML) to navigate the immense design space of material compositions and synthesis parameters (Waheed et al., 2024).

Predictive Modeling of Physicochemical and Biological Parameters

AI algorithms are being used to transform traditional “trial-and-error” experimentation into a predictive discipline. Supervised learning models, including random forest (RF), support vector machines (SVM), and extreme gradient boosting (XGBoost), can be trained on large experimental datasets to predict nanoparticle size, zeta potential, encapsulation efficiency (EE), and in vitro stability (Sabit et al., 2025).

A landmark study at Duke University utilized an automated wet-lab platform to generate 1,275 unique formulations, which were then used to train the TuNa-AI model. This approach resulted in a 42.9% increase in successful nanoparticle formation and led to the optimization of a venetoclax formulation that significantly outperformed the free drug in leukemia models (Liu et al., 2023).

Generative Design and AI-Powered Screening Platforms

Beyond predictive modeling, AI is facilitating the generative design of novel materials. Companies like METiS TechBio have developed the NanoForge platform, which utilizes a "lipid language model" to generate de novo ionizable lipids for lipid nanoparticle (LNP) libraries containing tens of millions of candidates. This has enabled the identification of organ-specific delivery systems targeting not just the liver, but also the lungs, heart, and central nervous system (Khan et al., 2021).

Table 3. Artificial Intelligence and Machine Learning Applications in Nanoparticle Drug Delivery System Optimization

AI / ML Application	Algorithm Type	Clinical / Research Impact
Formulation Optimization	Random Forest (RF), XGBoost, Artificial Neural Networks (ANN)	Predictive tuning of size, loading, and encapsulation efficiency (EE)
Protein Corona Prediction	LightGBM, XGBoost	Predicting biological identity and mononuclear phagocyte system (MPS) clearance
De Novo Material Discovery	Generative Models	Discovery of novel ionizable lipids for RNA delivery
Pharmacokinetic Modeling	Deep Learning (DL)	Modeling non-linear in vivo biodistribution
Real-Time Adaptive Dosing	Reinforcement Learning	Closed-loop optimization of stimuli-responsive drug release

The integration of multi-omics data with AI is also allowing for the conversion of tumor heterogeneity into quantitative design rules. By analyzing patient-specific genetic and proteomic profiles, AI can assist in the selection of the most effective targeting ligands and stimuli-responsive mechanisms for a given individual, paving the way for truly personalized precision oncology (Mainini & Eccles, 2020).

Clinical and Regulatory Landscape: 2024–2025 Milestones

The period of 2024–2025 has been marked by a significant influx of novel targeted therapies and the continued maturation of the nanomedicine regulatory framework (Khan et al., 2022).

Notable FDA Approvals and Pipeline Developments

While many approved "targeted" drugs are small molecules or antibodies, they are increasingly being formulated within nanoscale systems to enhance their therapeutic profile. 2024 saw the approval of Revumenib (Revuforj) for acute leukemia and Zolbetuximab (Vyloy) for gastric cancer the first antibody to target claudin 18.2 (Soomro et al., 2024). In early 2025, Zongertinib (Hernexeos) received accelerated approval for HER2-mutated non-small cell lung cancer (NSCLC), following results that showed a 75% objective response rate in patients previously treated with chemotherapy (Wang et al., 2021).

In the realm of nanotechnology proper, several gene-delivery and vaccine platforms have advanced to Phase III clinical trials. BioNTech's ROSETTA trial series is currently evaluating mRNA cancer immunotherapies delivered via lipid nanoparticles in combination with checkpoint inhibitors for both SCLC and NSCLC. Furthermore, METiS TechBio reported the successful completion of a Phase III trial for MTS-004, the world's first AI-enabled formulation to reach this milestone, reducing the development time from several years to just 38 months (Cojocaru et al., 2024).

Table 4. Recent FDA-Approved and Clinical-Stage Targeted Nanomedicine Therapeutics (2024–2025)

Approved / Pipeline Agent	Platform / Class	Indication	Approval / Status (2024-2025)
Revuforj (Revumenib)	Menin Inhibitor	KMT2A-rearranged Leukemia	FDA Approved (2024)
Vyloy (Zolbetuximab)	CLDN18.2 Antibody	Gastric/GEJ Adenocarcinoma	FDA Approved (2024)
Hernexos (Zongertinib)	HER2 TKI (Targeted)	HER2-mutated NSCLC	FDA Approved (2025)
Keytruda Qlex	Subcutaneous (Nano-formulated)	Multiple solid tumors	FDA Approved (2025)
BNT327	mRNA Bispecific (LNP)	Lung Cancer (SCLC/NSCLC)	Phase III (ROSETTA)
Hympavzi (Marstacimab)	Anti-TFPI Biologic	Hemophilia A/B	FDA Approved (2024)
MTS-004	AI-Optimized NDDS	Pseudobulbar Affect (CNS)	Phase III Complete

Regulatory Evolution and Challenges in Translation

Despite the scientific progress, clinical translation is still impeded by biological barriers and a fragmented regulatory landscape. The FDA currently regulates nanomedicines under existing frameworks for drugs, biologics, or devices, but with "heightened scrutiny" of nanoscale properties (Nie et al., 2023). The 2022 and 2024 updates to the "Guidance for Industry" emphasize that even small changes in manufacturing processes such as flow rates in microfluidic mixing or the purity of lipid excipients can fundamentally alter the safety and efficacy of the final product.

The lack of a formal legal definition for "nanomedicine" in the U.S. remains a point of uncertainty for developers (Sahai et al., 2021). Furthermore, establishing bioequivalence for generic nanomedicines (e.g., follow-on versions of Doxil or Abraxane) is challenging due to the complexity of characterizing "sameness" in terms of drug release and biodistribution at the nanoscale. Consequently, regulatory agencies are increasingly calling for "Quality-by-Design" (QbD) approaches, where sponsors must define critical quality attributes (CQAs) that link nano-properties directly to clinical performance (Chang et al., 2022).

Nanotheranostics: The Integration of Imaging and Therapy

The paradigm of theranostics the combination of diagnostic imaging and targeted therapy within a single nanoplatform is reaching a level of technological maturity that allows for the real-time monitoring and adaptation of treatment protocols (Abdessalem & Adham, 2024).

Multifunctional Radionuclide Platforms

Nuclear theranostics has emerged as a leader in this area, utilizing targeting vectors labeled with diagnostic radionuclides for molecular imaging (for example, gallium-68 and fluorine-18 for PET imaging) and therapeutic radionuclides for targeted radiation therapy (for example, lutetium-177 and actinium-225). Nanoplatforms such as liposomes, dendrimers, and inorganic gold or hafnium oxide particles are being engineered to carry these radionuclides deep into solid tumors (Zhou et al., 2021).

Hafnium oxide nanoparticles (for example, NBTXR3), which were approved by the European Medicines Agency in 2019, act as "radio-enhancers," where the nanoparticle interacts with ionizing radiation to increase the local radiation dose without increasing the external beam intensity (Firouzpour et al., 2026).

Real-Time Monitoring of Drug Distribution and TME Hypoxia

Advanced theranostic nanoparticles are now capable of monitoring tumor

hypoxia, a key driver of drug resistance and metastasis. By utilizing oxygen-sensitive nanoprobes and hypoxia-responsive MRI contrast agents, clinicians can visualize the physiological state of the tumor in real-time (Mostafa & Khojah, 2025). This enables a "feedback-driven" therapy model, where drug release can be triggered precisely when the tumor environment is most receptive, or where therapy can be adapted early if the imaging indicates poor target engagement (Rahman, 2025). The integration of nanotechnology with wearable devices and nanosensors is also an emerging trend for 2025, promising continuous health monitoring and early detection of cancer recurrence. These biosensors can detect circulating tumor DNA or specific biomarkers, alerting the clinician to the need for a targeted intervention before clinical symptoms appear (Chen, 2020).

Conclusion

In conclusion, nanoparticle-based targeted drug delivery systems represent a transformative advancement in cancer therapy by improving drug specificity, enhancing therapeutic efficiency, and reducing systemic toxicity. Through both passive and active targeting mechanisms, nanoparticles enable precise accumulation of therapeutic agents at tumor sites, thereby overcoming several limitations of conventional chemotherapy. The versatility of nanocarriers allows for multifunctional applications, including controlled drug release, combination therapy, and integration with diagnostic imaging for theranostic approaches. However, despite promising preclinical outcomes, several challenges such as potential nanotoxicity, immune system interactions, scalability issues, and regulatory constraints hinder widespread clinical adoption. Continued research is required to optimize nanoparticle design, improve biocompatibility, and ensure safe long-term use. Future developments in nanotechnology and biomedical engineering are expected to further enhance the clinical translation of these systems, ultimately contributing to more effective and personalized cancer treatment strategies.

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