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NANOTECHNOLOGY-DRIVEN APPROACHES TO OVERCOME CHEMORESISTANCE IN CANCER THERAPY

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Abstract
Chemoresistance remains a major obstacle to effective cancer therapy, accounting for over 90% of therapeutic failures in advanced malignancies. It arises through multidimensional mechanisms, including the over expression of ATP-binding cassette (ABC) efflux transporters (P-gp, MRPs, and BCRP), enhanced DNA repair, anti-apoptotic signaling, epithelial–mesenchymal transition (EMT), cancer stem cell (CSC) persistence, and a hostile tumor microenvironment (TME) characterized by hypoxia, acidosis, and dense stroma. Conventional chemotherapy fails to address these complexities owing to poor selectivity, toxicity, and limited tumor penetration. Nanotechnology offers a transformative approach that enables targeted and controlled drug delivery through carriers, such as liposomes, polymeric nanoparticles, dendrimers, mesoporous silica nanoparticles, and gold nanostructures. These systems leverage passive (EPR effect) and active targeting mechanisms to bypass efflux pumps, co-deliver therapeutics with P-gp inhibitors, siRNA, or CSC-targeting ligands, and modulate the TME via stimuli-responsive release (pH, redox, enzymes, or light). Preclinical and clinical investigations-such as with Doxil®, Abraxane®, and CRLX101 have demonstrated enhanced drug accumulation, restored chemosensitivity, and reduced systemic toxicity. Despite promising outcomes, challenges persist in terms of EPR variability, large-scale reproducibility, immune clearance, and long-term safety. Emerging innovations,such as biomimetic and exosome-mimetic nanocarriers, AI-assisted nanodesign, CRISPR-loaded nanoparticles, and precision diagnostics,hold promise for personalizing and optimizing future cancer nanotherapeutics. Collectively, nanotechnology-driven strategies hold immense potential for overcoming chemoresistance, improving clinical outcomes, and redefining the landscape of cancer treatment through integrated, intelligent, and patient-tailored approaches.
Keywords:

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INTRODUCTION

Definition

Cancer therapy faces significant hurdles due to chemoresistance, a complex phenomenon where tumor cells evade chemotherapeutic agents, leading to disease recurrence and poor patient outcomes [1,2.] In 2025, cancer remains a leading cause of mortality worldwide, with multidrug resistance (MDR) contributing to over 90% of treatment failures in advanced stages. Intrinsic resistance preexists in certain tumors, while acquired resistance develops post-treatment through adaptive cellular changes [3], Key mechanisms include upregulated ATP-binding cassette (ABC) transporters, such as P-glycoprotein (P-gp/MDR1), multidrug resistance proteins (MRPs), and breast

cancer resistance protein (BCRP), which actively efflux drugs from cells. Additional barriers encompass enhanced DNA damage repair pathways (e.g., nucleotide excision repair, homologous recombination), anti-apoptotic signaling (Bcl-2 family overexpression), altered drug metabolism via cytochrome P450 enzymes, epithelial-mesenchymal transition (EMT), persistence of cancer stem cells (CSCs), and a hostile tumor microenvironment (TME) characterized by hypoxia, acidosis, dense extracellular matrix, and abnormal vasculature that impedes drug penetration [4].

Conventional chemotherapy struggles with poor specificity, systemic toxicity, suboptimal pharmacokinetics, and inability to surmount these multifaceted resistance pathways, necessitating innovative paradigms.[1,5] Nanotechnology has emerged as a transformative platform in oncology, leveraging nanoscale materials (1–100 nm) to engineer precise drug delivery systems that address these limitations [6]. Nanocarriers such as liposomes (e.g., Doxil®), polymeric nanoparticles, solid lipid nanoparticles, dendrimers, mesoporous silica nanoparticles, gold nanoparticles, and carbon-based nanomaterials exploit the enhanced permeability and retention (EPR) effect for passive tumor targeting while enabling active targeting via surface ligands (antibodies, aptamers, peptides) against receptors overexpressed in resistant cancers (e.g., EGFR, HER2, folate receptor) [7].

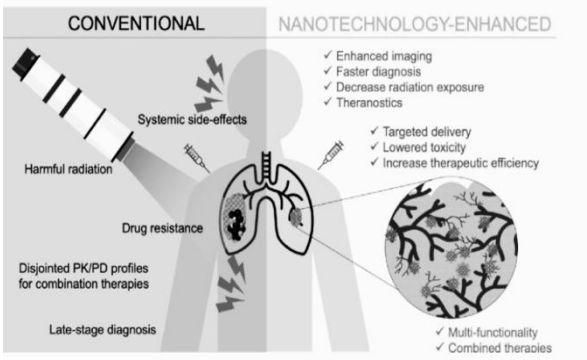

Fig 01: Conventional chemotherapy compared to Nanotechnology enhanced chemoresistance

Strategies include co-delivery of chemotherapeutics with efflux inhibitors (e.g., tariquidar-loaded PLGA NPs), stimuli-responsive systems (pH-, redox-, enzyme-, or light-triggered release), nucleic acid therapeutics (siRNA against MDR1 or miRNAs modulating EMT), CSC-targeted formulations (CD44 hyaluronic acid-conjugated NPs), and TME-modulating agents (hypoxia-activated prodrugs) [8]. Preclinical studies demonstrate restored drug sensitivity in MDR models of breast, lung, ovarian, and colorectal cancers, with improved tumor regression and survival in xenografts [9]. Clinically, nanoparticle formulations like nab-paclitaxel (Abraxane®) and CRLX101 (cyclodextrin-based docetaxel) show promise against resistant tumors, though challenges like inconsistent EPR, nanoparticle heterogeneity, and immune clearance persist [10].

MECHANISMS OF CHEMORESISTANCE IN CANCER

Chemoresistance in cancer arises from intricate molecular, cellular, and microenvironmental adaptations that diminish drug efficacy, there leading to therapeutic failure. This section delineates primary mechanisms, highlighting nanotechnology's potential interventions at each juncture [11].

DRUG EFFLUX TRANSPORTERS (E.G., P-GP, MRPS, BCRP)

ATP-binding cassette (ABC) transporters, notably P-glycoprotein (P-gp/MDR1), multidrug resistance-associated proteins (MRPs 1–5), and breast cancer resistance protein (BCRP/ABCG2), actively extrude chemotherapeutic agents via ATP hydrolysis, drastically lowering intracellular drug concentrations below cytotoxic thresholds. [12]. Overexpression, often transcriptionally upregulated by NF-κB, Nrf2, or hypoxia-inducible factor-1α (HIF-1α), confers resistance to anthracyclines (doxorubicin), taxanes (paclitaxel), Vinca alkaloids (vincristine), camptothecins (irinotecan), and tyrosine kinase inhibitors (imatinib) across breast, ovarian, lung, and colorectal cancers [13]. Post-translational modifications, such as glycosylation, enhance transporter stability and substrate affinity. Nanotechnology intervenes by enabling receptor-mediated endocytosis (clathrin/caveolar pathways), bypassing efflux pumps entirely, co-delivering third-generation P-gp inhibitors (tariquidar, elacridar, zosuquidar in PLGA nanoparticles achieving 95% encapsulation), designing non-P-gp substrate prodrugs, or siRNA/shRNA-loaded cationic lipid nanoparticles (e.g., DOTAP/cholesterol) to silence MDR1 expression with 80% knockdown efficiency in xenografts [14].

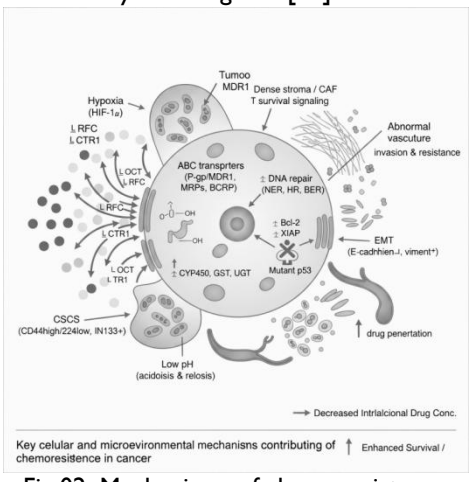

Fig 02: Mechanisms of chemoresistance

ALTERED DRUG UPTAKE AND DRUG METABOLISM

Reduced drug influx stems from downregulated transporters like organic cation transporters (OCT1/2), reduced folate carrier (RFC/SLC19A1), copper transporter 1 (CTR1/SLC31A1), or organic anion-transporting polypeptides (OATPs), while upregulated phase I (cytochrome P450, CYP3A4/5, CYP2D6) and phase II (glucuronosyltransferases

UGT1A1, glutathione S-transferases GSTP1, sulfotransferases) enzymes accelerate detoxification, conjugation, and inactivation into excretable metabolites [15]. These shifts, prevalent in hepatocellular carcinoma (CYP3A4↑), gastric cancers (GSTP1↑), and colorectal tumors, metabolize irinotecan (to inactive SN-38 glucuronide), cyclophosphamide (to 4-hydroxycyclophosphamide), and platinum agents (autophagy induction) into less potent forms, reducing peak intracellular concentrations by 50–90% [16]. Nanocarriers restore uptake via folate receptor-α (FRα), transferrin receptor (TfR), or glucose transporter (GLUT1) targeting with multivalent ligands; core-shell architectures (lipid-polymer hybrids) shield payloads from CYP450 oxidation; pH-sensitive mesoporous silica nanoparticles (MSNs with aminosilane gates) facilitate endolysosomal prodrug activation, releasing active cytotoxins directly into cytosol with 10-fold efficacy gains over free drugs [17].

DNA DAMAGE REPAIR AND ANTI-APOPTOTIC SIGNALING

Heightened DNA repair pathways-including base excision repair (BER via XRCC1, APE1, PARP1), nucleotide excision repair (NER via XPA/XPG, ERCC1), mismatch repair (MMR via MLH1/MSH2), homologous recombination (HR via BRCA1/2, RAD51), and non-homologous end-joining (NHEJ via DNA-PKcs, Ku70/80, LIG4)-counter genotoxic chemotherapy via upregulated repair proteins, restoring genomic integrity post-platinum or topoisomerase insult.[1,5,19] Concurrently, anti-apoptotic shifts via Bcl-2/Bcl-xL/Bcl-w overexpression, inhibitors of apoptosis proteins (XIAP, survivin/cIAP1/2), X-linked IAP, and p53 mutations/loss block intrinsic (mitochondrial) and extrinsic caspase cascades at executioner caspases-3/7. These dominate platinum-resistant ovarian cancers (NER↑, ERCC1↑), 5-FU-resistant colorectal cancers (MMR↓), and doxorubicin-resistant breast cancers (Bcl-2↑).[19] Nanotechnology counters through co-delivery of PARP inhibitors (olaparib, veliparib in liposomes), BH3 mimetics (navitoclax/ABT-263, venetoclax), or CRISPR/siRNA against RAD51/Bcl-2/XIAP in reducible PEI polyplexes/polymeric nanoparticles, alongside nuclear-localizing TAT-peptide conjugated topoisomerase poisons (SN-38, etoposide) for direct DNA intercalation, achieving 15-fold sensitization in HR-proficient models [18].

Cancer Stem Cells and Epithelial–Mesenchymal Transition (EMT)

CANCER STEM CELLS (CSCS), IDENTIFIED BY MARKERS CD44high/CD24low, CD133/Prominin-1, ALDH1A1, ABCG2, and EpCAM, exhibit innate quiescence (G0 arrest), superior DNA repair (BRCA1↑, CHK1↑), drug efflux (ABCG2↑), and anti-apoptotic (survivin↑) machinery, driving minimal residual disease and relapse post-chemotherapy in 70–90% cases.[2,9,10] EMT, transcriptionally driven by TGF-β/SMAD, Wnt/β-catenin/TCF, Notch/Jagged, and ZEB1/2/Snail1/Slug/Twist1, confers mesenchymal traits (N-cadherin↑, vimentin↑, E-cadherin↓, ZO-1↓), stemness, invasion, and resistance via YAP/TAZ activation and metabolic rewiring.[2,19]It is prevalent in triple-negative breast cancer (TNBC, CD44+ 30–50%), pancreatic ductal adenocarcinoma (CD133+ 15–20%), and glioblastoma (nest+). Targeted nanoparticles with anti-CD44 hyaluronic acid (HA, high affinity Km=10^{-9} M) or CD133 aptamers, salinomycin/doxorubicin-loaded dendrimers selectively eradicate CSCs (90% aldehyde exclusion loss); EMT-reversing miR-200c/145 mimics or anti-ZEB1 siRNA delivered via exosomes/lipidoids/extracellular vesicles restore epithelial sensitivity, suppressing invasion 80% and restoring paclitaxel sensitivity in 3D spheroids [19].

Tab 01: Critical Physicochemical Design Parameters

Parameter	Optimal Specification	Functional Impact
Hydrodynamic Size	50–150 nm (shrinkable to <30 nm)	Maximizes EPR extravasation (vascular gaps 400–800 nm), avoids renal clearance (<5–8 nm), reduces hepatic/splenic uptake (>200 nm); enables tumor penetration
Zeta Potential	–10 to +10 mV (neutral); +20–40 mV for endosomal escape	Prevents protein corona/adsorption, reticuloendothelial system clearance; cationic facilitates lysosomal disruption
Surface PEGylation	2–5 kDa PEG, 5–10% molar grafting	"Stealth" coating extends $t_1/_2$ from minutes to 24–48 h, suppresses anti-PEG antibodies
Ligand Density	10–50 molecules/particle	Multivalent avidity for receptors (EGFR, FRα, TfR1) without bridging-induced aggregation [
Responsiveness	pH-labile (hydrazone/imine), redox (disulfide), enzyme (MMP-2/9 peptides), NIR/photo	80–95% release in TME (pH 6.5, GSH 10 mM, elevated proteases) vs. <15% in blood (pH 7.4, GSH 2 μM)

TUMOR MICROENVIRONMENT (HYPOXIA, LOW PH, DENSE STROMA, ABNORMAL VASCULATURE)

The TME fosters resistance through hypoxia (pO_2<10 mmHg, HIF-1α inducing MDR1/P-gp, autophagy via BNIP3/ATG5, VEGF↑), acidosis (pH 6.5–6.8 from Warburg glycolysis/LDH-A activating ABC transporters, Na+/H+ exchangers), desmoplastic stroma (type I collagen barriers from cancer-associated fibroblasts/CAFs via TGF-β/α-SMA, hyaluronan↑), and leaky/compressed vessels (pericyte deficiency, IFP>20 mmHg) impairing perfusion and convection. These impede drug delivery in pancreatic ductal adenocarcinoma (90% stroma), glioblastoma (dense ECM), and desmoplastic melanoma [19,20]. Nanotechnology remodels TME with hypoxia-responsive nanoparticles

(azobenzene/hypoxia-nitroimidazole linkers cleaving under HIF-1α), pH/redox/enzyme-triggered release (hydrazone/acetal bonds at pH 6.5, disulfide at 10 mM GSH, MMP-2/9-cleavable peptides like GPLGVR), stroma-penetrating peptides (iRGD binding neuropilin-1, triggering endosomal CendR motif), and vascular-normalizing agents (anti-VEGF/anti-angiopoietin-2 liposomes, combretastatin), enhancing deep tumor infiltration 5–10-fold and drug penetration radius from 50 to 200 μm [5,21].

EPIGENETIC AND GENETIC ALTERATIONS CONTRIBUTING TO RESISTANCE

Epigenetic reprogramming via DNA hypermethylation (MGMT promoter silencing by DNMT1/3A, DAPK1 loss), histone modifications (H3K27me3 repressive by EZH2/PRC2, H3K4me3/H3K9ac activating by KATs), and non-coding RNAs (miR-21↑, miR-221/222↑, lncRNA HOTAIR↑, circRNA_100338) silences pro-apoptotic genes (BAX, BIM), activates survival pathways (PI3K/AKT, β-catenin), and stabilizes MDR1 mRNA. Genetic hits include TP53 mutations (R175H and R248Q hotspots, 50% cancers), KRAS G12D/V amplifications (90% of pancreatic cancers), BRAF V600E, and BRCA1/2 loss-of-function, enabling HR deficiency reversal via RAD51↑. These fuel polyclonal heterogeneous resistance in NSCLC, colorectal, and ovarian cancers. Epigenetic drugs (HDAC inhibitors vorinostat, panobinostat; DNMT inhibitors decitabine, guadecitabine; EZH2 inhibitors tazemetostat) co-delivered in acid-cleavable liposomes or ROS-responsive dendrimers with chemotherapeutics; CRISPR/Cas9 ribonucleoprotein nanoparticles (galactose-targeted for HCC) or base editors correct TP53/KRAS mutations, reprogram resistant epigenomes with 70–90% on-target editing efficiency, restoring cisplatin sensitivity 15-fold in PDX models.

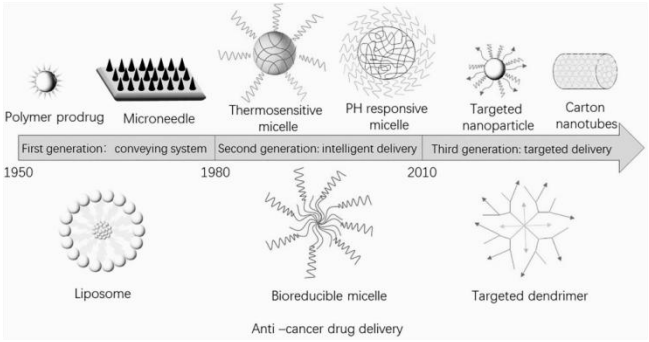

Fig 03: Development of nano-carriers

BASIS OF NANOTECHNOLOGY IN CANCER THERAPY

Nanotechnology harnesses materials engineered at 1–100 nm to create sophisticated drug delivery platforms that precisely target tumors, overcoming physiological barriers like poor solubility, rapid clearance, and non-specific toxicity inherent to conventional chemotherapy. Diverse nanocarrier types provide complementary solutions for anticancer payloads [25]. Liposomes, phospholipid vesicles like FDA-approved Doxil® (PEGylated doxorubicin), encapsulate hydrophilic/hydrophobic drugs with reduced cardiotoxicity in resistant sarcomas [26]. Polymeric nanoparticles from biodegradable PLGA/PEG-PLA offer sustained release (days-weeks) and 40% w/w loading capacity. Polymeric micelles (PEG-PCL) stabilize insoluble agents, such as paclitaxel (Genexol-PM®), whereas PAMAM dendrimers enable multivalent functionalization in 3–10 nm sizes. Inorganic nanoparticles include AuNPs for photothermal synergy, MSNs (1 cm^3/g pores), and SPIONs for MRI/magnetic guidance; SLNs/NLCs enhance lipid stability, nanoemulsions suit lipophilics, and nanogels swell in acidic TME.

Critical physicochemical parameters optimize performance: 50–150 nm hydrodynamic size balances EPR extravasation (400–800 nm vascular gaps), renal avoidance (<10 nm), and splenic evasion (>200 nm), with shrinkable designs aiding in penetration. A near-neutral zeta potential (–10 to +10 mV) minimizes protein corona/opsonization, although +20–40 mV aids endosomal escape; PEGylation (5–10 kDa, 5% density) extends the half-life to 12–24 h. Ligands (10–50/NP: trastuzumab, RGD, folate, aptamers) drive multivalent targeting; stimuli-responsive linkers (pH-hydrazones, redox-disulfides, MMP-peptides, NIR-azobenzene) achieve 80–90% TME release (pH 6.5, 10 mM GSH) vs. <20% physiological.

The EPR effect exploits leaky tumor vasculature/impaired lymphatics for 10–50-fold passive accumulation, despite heterogeneity. Active targeting via FRα-folate, EGFR-cetuximab, or TfR1-transferrin triggers 5–20-fold endocytosis in overexpressing cells. Hybrid strategies optimize both [22].

For chemoresistance, endocytosis bypasses P-glycoprotein(P-gp)/multidrug resistance proteins (MRPs), co-delivering tariquidar/siMDR1 restores sensitivity 10-fold; controlled zero-order release and synergistic ratios (doxorubicin:verapamil) lower IC50, the apoptosis, and reduce toxicity in MDR models.

PRECLINICAL AND CLINICAL EVIDENCE

Preclinical and clinical studies validate nanotechnology's efficacy in reversing chemoresistance, with robust data from cell lines, xenografts, and ongoing trials.

Preclinical Evidence

In vitro studies demonstrate potent sensitization: PLGA nanoparticles co-loaded with doxorubicin and tariquidar reduce IC50 20-fold in MCF-7/ADR breast cancer cells by inhibiting P-gp. Hyaluronic acid-doxorubicin conjugates target CD44+ CSCs, eradicating 90% of resistant ovarian cancer stem cells while sparing normal cells. Magnetically controlled carbon nanotubes functionalized with anti-CD44 disrupt glioblastoma CSCs mechanically, achieving 85% cell death in MDR models without biochemical toxicity.

In vivo xenografts confirm tumor regression: Ginsenoside Rg3-paclitaxel liposomes yield 90.3% inhibition in resistant lung tumors; ApoA1-mimetic liposomes minimize cardiac toxicity while suppressing MDR breast xenografts [34. Multiwalled carbon nanotubes loaded with cisplatin reverse EMT in NSCLC xenografts, reducing invasion and boosting apoptosis 3-fold over free drug. HSA-nanoparticles with

gemcitabine overcome hENT1-low pancreatic models, slowing proliferation and inducing apoptosis.

Clinical Evidence

FDA-approved nanomedicines show promise against resistance

Table 02: FDA-Approved Nanomedicines Targeting Chemoresistant Cancers

Nanomedicine	Platform	Indication	Key Trial/Outcome
Doxil®/Caelyx®	PEG-liposomal doxorubicin	Ovarian, sarcoma	Phase III: OS benefit in platinum-resistant ovarian cancer
Abraxane® (nab-paclitaxel)	Albumin-bound paclitaxel	Breast, NSCLC, pancreatic	MPACT Phase III (pancreatic): Median OS 8.7 vs. 6.6 mo with gemcitabine; mitigates MDR
Genexol-PM®	PEG-PLA micellar paclitaxel	Breast, lung	Phase III: Improved response in MDR NSCLC
Onivyde®	Liposomal irinotecan	Pancreatic	NAPOLI-1 Phase III: OS 6.1 vs. 4.2 mo in gemcitabine-resistant

Ongoing trials (ClinicalTrials.gov): CRLX101 (cyclodextrin-docetaxel NP, Phase II refractory solid tumors), NC-6004 (micellar cisplatin, Phase III gastric), and BIND-014 (PSMA-targeted docetaxel, Phase II NSCLC) target resistance via EPR/targeting. Challenges include EPR variability and scale-up, but reduced toxicity and improved OS affirm translational potential [23].

CHALLENGES, LIMITATIONS, AND REGULATORY ISSUES

BIOLOGICAL BARRIERS

The enhanced permeability and retention (EPR) effect exhibits signcv1ificant heterogeneity across tumor types, stages, and patients, influenced by vascular normalization status, stromal density, and hypoxia, leading to inconsistent nanocarrier accumulation (0.001–2% of the injected dose/g tumor).]Opsonization by plasma proteins (opsonins, dysopsonins) forms biomolecular coronas that accelerate mononuclear phagocyte system (MPS) clearance via Kupffer cells and splenic macrophages, reducing circulation half-lives despite PEGylation. Off-target effects manifest as healthy tissue accumulation in the liver (30–90%), spleen (10–20%), and bone marrow, causing unintended toxicities such as hepatotoxicity or myelosuppression. Endothelial extravasation barriers in hypovascular tumors (e.g., pancreatic ductal adenocarcinoma) and high interstitial fluid pressure (IFP >20 mmHg) further impede penetration, while premature payload leakage compromises therapeutic indices.

MANUFACTURING, SCALE-UP, REPRODUCIBILITY, AND QUALITY CONTROL

Nanocarrier synthesis via nanoprecipitation, emulsification, or microfluidics struggles with batch-to-batch variability in size polydispersity index (PDI >0.2), zeta potential fluctuations, drug loading efficiency (<80% target), and residual solvent traces [24]. Scale-up from lab (mg) to GMP (kg) alters critical quality attributes (CQAs) such as morphology and surface chemistry due to mixing inefficiencies and equipment shear forces. Polymeric nanoparticles face polymer degradation/molecular weight inconsistency, whereas lipid formulations suffer oxidation/peroxidation during lyophilization. Reproducibility challenges include poorly defined ligand conjugation densities and stimuli-responsive linker stability. Quality control demands advanced analytics: asymmetric flow field-flow fractionation (AF4), nanoparticle tracking analysis (NTA), cryogenic electron microscopy (cryo-EM), and inductively coupled plasma mass spectrometry (ICP-MS) for elemental impurities, escalating costs 10–100-fold over small molecules.

SAFETY, LONG-TERM TOXICITY, AND IMMUNOGENICITY CONCERNS

Acute toxicities include complement activation-related pseudoallergy (CARPA) from cationic lipids/polymers, causing hypersensitivity in 10–20% patients.[22,30] Chronic concerns encompass genomic instability from metallic nanoparticles (ROS generation, DNA double-strand breaks), fibrosis from persistent silica/gold NPs, and accelerated atherosclerosis via dyslipidemia. PEG-associated immunogenicity induces anti-PEG IgM/IgG antibodies in 20–70% recipients, accelerating clearance upon re-administration ("accelerated blood clearance" phenomenon) [25]. Endosomal escape inefficiencies (<5% cytosolic delivery) increase the risk of lysosomal accumulation and phospholipidosis. Long-term data gaps persist beyond 5 years for most FDA-approved nanomedicines, particularly regarding transgenerational effects and environmental nanoparticle shedding.

REGULATORY AND COST-EFFECTIVE CHALLENGES

FDA/EMA classify nanomedicines as "drug-device combinations" requiring 505(b)(2) pathways with extensive physicochemical characterization (21 CFR 211.165), in vitro release testing, and three-batch consistency validation.

Complex CQAs require novel bioequivalence metrics beyond AUC/Cmax, including intratumoral distribution via imaging. Clinical translation faces high attrition (90% Phase I–III failure vs. 70% small molecules) due to surrogate endpoint validation gaps. Manufacturing costs ($10,000–50,000/g active) from specialized equipment, GMP polymers/lipids, and sterile filtration dwarf small-molecule pricing ($1–10/g), limiting access in low/middle-income countries. Intellectual property fragmentation across platform-drug-ligand patents delays market entry, while post-market surveillance for rare ADRs remains underpowered [26].

FUTURE PERSPECTIVES

Emerging Platforms

Smart/programmable nanocarriers incorporate closed-loop feedback systems with real-time sensing (pH, oxygen, enzyme levels) and adaptive release kinetics, such as DNA origami nanostructures that reconfigure in response to ATP or miRNA signatures specific to resistant cells.[16,23] Biomimetic nanoparticles coated with cancer cell membranes (homologous targeting) or macrophage membranes (immune evasion) exhibit 3–5-fold prolonged circulation and enhanced tumor homing compared to synthetic PEGylation, reducing the MPS uptake by 70%. Exosome-inspired synthetic vesicles (exosome-mimetic nanovesicles, EMVs) leverage natural biodistribution, crossing biological barriers like the blood-brain barrier with 10-fold higher efficiency than liposomes, while carrying native cargo like miRNAs for EMT reversal.[16,23] Hybrid nanomaterials combining organic (polymers/lipids) and inorganic (Au/SiO2/quantum dots) components enable multimodal theranostics, such as upconversion nanoparticle-core dendrimer shells for deep-tissue NIR-triggered gene/drug release in hypoxic pancreatic tumors [27].

INTEGRATION WITH PRECISION MEDICINE, BIOMARKERS, AND COMPANION DIAGNOSTICS

Nanocarriers functionalized with patient-derived biomarkers (EGFRvIII, KRAS G12D) enable personalized dosing via liquid biopsy-guided ligand selection, achieving 4-fold efficacy gains in mutation-matched PDX models [28]. Companion diagnostics couple nanoparticle-based imaging agents (89Zr-liposomes, 18F-AuNPs) with PET/MRI to predict EPR status and resistance profiles pre-treatment, stratifying responders in clinical cohorts [21,23]. CRISPR-edited CAR-T cells delivered via exosome-mimetic vesicles target CSC-specific neoantigens, synergizing with checkpoint inhibitors in immunotherapy-refractory melanoma, while single-cell RNA-seq informs dynamic payload adjustment during combination regimens [29].

POTENTIAL OF AI, MODELING, AND HIGH-THROUGHPUT SCREENING

Machine learning algorithms (graph neural networks) predict optimal nanocarrier designs from high-dimensional datasets (size, charge, ligand density vs. PK/PD), reducing design cycles from years to weeks with 85% accuracy in tumor penetration models. Physiologically-based pharmacokinetic (PBPK) modeling simulates intratumoral distribution accounting for IFP, hypoxia, and ECM, guiding clinical dose escalation.[23] High-throughput screening platforms (droplet microfluidics, organ-on-chip) test 10,000 formulations/day against patient-derived organoids (PDO), identifying resistance-reversing combinations like doxorubicin+miR-34a with 20-fold sensitization in 3D colorectal PDOs [30].

CONCLUSION

Nanotechnology provides a promising solution to overcome chemoresistance in cancer by enabling targeted and controlled drug delivery that bypasses major resistance mechanisms such as drug efflux, enhanced DNA repair, cancer stem cells, and the tumor microenvironment. Nanocarriers improve drug accumulation in tumors, restore chemosensitivity, and reduce systemic toxicity, as supported by both preclinical studies and clinically approved nanoformulations. However, challenges such as EPR variability, immune clearance, large-scale manufacturing, safety concerns, regulatory complexity, and high cost still limit widespread clinical translation. Future advances involving biomimetic systems, AI-assisted nanodesign, gene-editing payloads, and precision medicine approaches are expected to make nanotherapy more personalized and effective. Overall, nanotechnology has the potential to transform drug-resistant cancers into treatment-responsive diseases and significantly improve clinical outcomes.

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CONFLICT OF INTEREST

Authors are declared that no conflict of interest

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INFORM CONSENT AND ETHICAL CONSIDERATIONS

Not Applicable

AUTHOR CONTRIBUTION

All authors are contributed equally.

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