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Review

Nanomedicine Strategies to Overcome Multi-Drug Resistance in Cancer: Innovations in Targeted Delivery, Tumor Microenvironment Modulation and Synergistic Therapies

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Abstract

Multi-drug resistance (MDR) remains a major health challenge in the cancer treatment, leading to treatment failure and disease recurrence. Recent advancements in nanomedicine have introduced innovative approaches to treat MDR by improving drug delivery, reducing systemic toxicity, and re-sensitizing resistant cancer cells. This review provides a comprehensive summary of various nanocarrier systems that have been developed to bypass drug efflux mechanisms, promote intracellular drug accumulation, and permit controlled release. These nanocarrier systems include liposomes, polymeric nanoparticles, metal-based nanoparticles, and supramolecular constructs. Additionally, we discuss approaches targeting the tumor microenvironment, such as reprogramming tumor-associated macrophages (TAMs), reversing immunosuppression, and manipulating cancer stem cell differentiation. Special attention is paid to co-delivery systems that combine chemotherapeutics with gene therapies, redox-active compounds, autophagy inhibitors, and nitric oxide donors to produce synergistic anticancer effects. Novel strategies such as ferroptosis-inducing nanodrugs, stimuli-responsive platforms, and ultrasonic or photothermic based improved therapies are emphasized for their ability to evade typical resistance pathways. We also go over the important examples where nanotechnology has been utilized to counter MDR specifically in colorectal, ovarian, glioblastoma, and non-small cell lung cancer, targeting mechanisms such as P-glycoprotein overexpression, MRP2 transport, MGMT-mediated repair, and EGFR-TKI resistance. While promising preclinical results highlight the translational potential of nanomedicine for overcoming MDR, clinical integration remains a challenge. Key obstacles include scalable manufacturing, regulatory alignment, and thorough safety validation. This review aims to inform the rational design and clinical translation of nanotechnology-enabled therapeutics for drug-resistant cancers by integrating mechanistic insights with nanoplatform innovation.

Keywords: nanomedicine; multidrug resistance; co-delivery systems; tumor microenvironment (TME); drug efflux inhibition; stimuli-responsive nanoparticles; cancer immunotherapy; siRNA delivery; ferroptosis; targeted drug delivery

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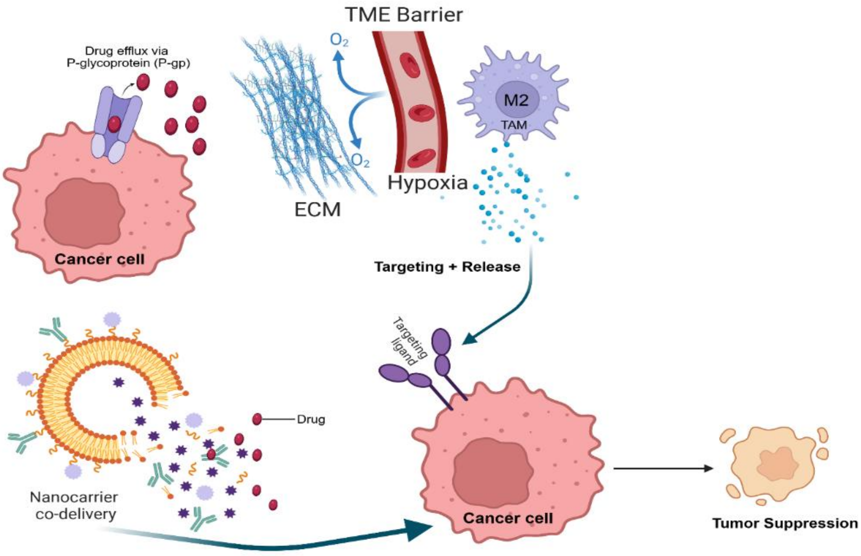

Graphical Abstract

1. Introduction

Cancer is a leading cause of global mortality, with ~20 million new cases and 9.7 million deaths in 2022 [1–3]. A major obstacle in effective cancer therapy is multidrug resistance (MDR), where tumors become refractory to chemotherapy, targeted agents, or radiation. In fact, up to ~90% of chemotherapy failures are attributed to acquired resistance mechanisms [4,5]. MDR arises from complex biochemical and cellular adaptations that allow cancer cells to evade drug-induced cytotoxicity. These include upregulated drug efflux pumps (e.g. P-glycoprotein), enhanced DNA repair, apoptosis suppression, and influences from the tumor microenvironment (TME) [6–8]. Overcoming MDR is critical to improve patient outcomes. In recent years, nanomedicine has emerged as a transformative approach to counter MDR by improving drug delivery and enabling novel combination therapies. The clinical shift toward precision, low-toxicity interventions—such as HPV-HR DNA testing for posttreatment cancer monitoring [9,10] parallels the rise of nanomedicine strategies for overcoming treatment resistance. Engineered nanoparticles (NPs) can preferentially accumulate in tumors via the enhanced permeability and retention (EPR) effect, be surface modified with targeting ligands, and co-encapsulate multiple agents (e.g. a chemotherapeutic plus an MDR modulator or gene therapy) for synergistic action [11,12]. Nanocarriers can also be designed to release cargo in response to tumor-specific stimuli (pH, enzymes, light, ultrasound), and to modulate the TME (e.g. reprogramming macrophages or degrading stroma) [11,13,14]. These properties help to evade efflux pumps, bring back drug sensitivity, and improve antitumor immunity. These capabilities uniquely position nanomedicine as a multifaceted tool to counteract resistance at the molecular, cellular, and microenvironmental levels.

This review provides a comprehensive, up-to-date analysis of the molecular mechanisms underlying MDR in cancer alongside emerging nano-strategies to address them. We begin by discussing the cellular and molecular and biochemical foundation of MDR, including drug efflux transporters, apoptotic evasion, and tumor heterogeneity. We then explore a range of advanced nanocarrier platforms, targeted delivery tactics, co-delivery systems, and stimuli-responsive therapies that jointly overcome resistance. Throughout, we emphasize molecular mechanisms and translational potential, highlighting biochemical targets (e.g. ABC transporters, apoptosis regulators) and preclinical/clinical innovations in nanomedicine for MDR [6,15,16]. Emerging modalities such as ferroptosis-inducing nanoparticles, nitric oxide (NO) releasing platforms, and photothermal/ultrasound-triggered nanotherapies are also examined. Finally, we outline the key

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translational challenges and propose future directions to facilitate the clinical adoption of nanomedicine in the therapy of MDR cancers.

2. Mechanisms of MDR in Cancer

Tumor cells evade therapy through multiple, often overlapping mechanisms, as detailed in recent comprehensive reviews [6]. The principal categories are:

2.1. Drug Efflux Transporters

Upregulation of ATP-binding cassette (ABC) pumps is a hallmark of MDR. P-glycoprotein (P-gp/ABCB1) is the most studied efflux pump [6]. Cryo-EM studies reveal conformational changes during substrate transport that underline its broad specificity [6,17]. Other ABC proteins such as MRP1/ABCC1 and BCRP/ABCG2 contribute to resistance against chemotherapies and targeted drugs [6,16]. For example, MRP1 can export kinase inhibitor metabolites, and BCRP confers resistance to several targeted agents [17,18]. Notably, cells can dynamically regulate transporter levels: recent data show that resistant cells reprogram ABC expression profiles under drug stress [6]. Stromal signals also impact efflux: cancer-associated fibroblasts (CAFs) can induce tumor cell ABC expression via paracrine pathways, creating a protective niche [6,19]. High efflux activity prevents intracellular drug accumulation, so inhibiting or bypassing these pumps is key to overcoming MDR. However, most platforms remain in the early translational phase, with few having progressed to clinical trials.

2.2. Apoptosis Evasion

Cancer cells often disable programmed cell death to survive therapy [6,20,21]. Overexpression of anti-apoptotic BCL-2 family proteins (BCL-2, BCL-XL, MCL-1) is commonly observed in resistant tumors [22]. Advanced proteomics show these proteins are post-translationally stabilized in MDR cells, strengthening survival [23]. Similarly, the IAP family (e.g. XIAP, cIAP1) inhibits caspases; elevated XIAP correlates with poor response to platinum chemo in ovarian cancer [24]. Tumors also inactivate p53: beyond gene mutations, recent studies identified novel posttranslational modifications of p53 that impair its apoptotic function [25]. Tumor cells can further rewire mitochondrial dynamics (increasing fusion, reducing cytochrome c release) to block intrinsic apoptosis [26,27]. They may also downregulate death receptors (FAS, TRAIL receptors) on the cell surface, evading extrinsic apoptosis [28,29]. Importantly, the TME enforces survival: CAFs and other stromal cells secrete cytokines (e.g. IL-6, IGFs) that upregulate anti-apoptotic proteins in cancer cells [30,31]. Together, these adaptations mean drugs that rely on apoptosis (most chemotherapies) become ineffective.

2.3. Enhanced DNA Repair

Many cytotoxic agents work by inducing DNA damage; resistant tumors often boost repair pathways. For instance, repeated genotoxic stress selects for cancer cells with upregulated homologous recombination and non-homologous end joining (NHEJ) repair proteins [32]. Single-cell analyses reveal plasticity: subclones with heightened DNA damage response (DDR) survive therapy, leading to radio- and chemo-resistant populations [33,34]. Cancer stem-like cells, often drug-resistant, inherently exhibit superior DNA repair and antioxidant defenses [33]. Enhanced nucleotide excision repair or base-excision repair can remove drug-induced lesions before apoptosis is triggered. Thus, inhibiting key repair enzymes (e.g. PARP, ATR) is explored to sensitize MDR tumors.

2.4. Tumor Microenvironment (TME)-Induced Resistance

The TME comprises stromal fibroblasts, immune cells (macrophages, myeloid cells), extracellular matrix (ECM), and factors like hypoxia and acidity, all of which influence drug response [35,36]. Hypoxic regions in tumors stabilize HIF-1α, which promotes cell survival pathways and selection of aggressive, stem-like cells [37]. Hypoxia also impairs drug penetration and immune

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function [38]. CAFs secrete ECM components (collagen, fibronectin) that increase tissue stiffness and form a physical barrier, limiting drug diffusion. They also release growth factors (TGF-β, IL-6) that activate pro-survival signaling in cancer cells [39]. Similarly, tumor-associated macrophages (TAMs) often polarize to an M2-like phenotype under TME cues, releasing IL-10, VEGF and proteases that support tumor growth, angiogenesis, and matrix remodeling [40]. MDSCs and regulatory T cells in the TME suppress anti-tumor immunity and can secrete metabolites (e.g. arginase, IDO) that reduce drug efficacy. Metabolic competition (e.g. for glucose) in the TME also stresses effector immune cells while tumor cells adapt [41]. These TME factors effectively create a fortress around tumor cells, promoting quiescence and resistance.

2.5. Epigenetic Reprogramming

Reversible changes in gene expression contribute to MDR. For example, alterations in DNA methylation or histone modification can silence tumor suppressors or activate survival genes. Recent findings show that epigenetic changes can swiftly reprogram cells to use bypass pathways under therapy [42]. Cancer cells undergoing drug tolerance states display unique chromatin landscapes that prime them for resistance. For instance, histone methylation changes may activate drug efflux or DNA repair genes. MicroRNAs and long noncoding RNAs also modulate MDR by targeting ABC transporters or apoptotic genes. Such epigenetic plasticity enables tumors to adapt transiently to drugs and later re-sensitize after drug withdrawal, complicating therapy [43,44].

In summary, MDR arises from the interplay of intrinsic tumor cell adaptations and extrinsic TME factors, enabling tumors to escape multiple therapies. Effective strategies must therefore multitask; suppress efflux, restore apoptosis, block repair, and re-engineer the TME. Nanomedicine is uniquely suited to this challenge.

3. Strategies to Overcome Multidrug Resistance

3.1. Nanocarriers Inhibiting Drug Efflux Pumps (P-gp, MRP2, etc.)

One fundamental approach to overcoming multidrug resistance (MDR) is to inhibit or evade the ATP-binding cassette (ABC) efflux transporters such as P-glycoprotein (P-gp/ABCB1), MRP1/MRP2, and BCRP. Recent nanocarrier systems have been designed to co-deliver chemotherapeutics with efflux pump inhibitors or siRNAs to suppress these transporters' function or expression [45–47]. Encapsulating drugs in nanoparticles can bypass recognition by efflux pumps and even target the cell nucleus, thereby increasing intracellular drug retention. For example, polymeric micelles carrying doxorubicin (DOX) together with a P-gp siRNA showed effective P-gp gene silencing and restored drug sensitivity in resistant cancer cells [48,49]. Another strategy is using nanocarriers that disrupt cancer cell energy supply: a mitochondria-targeted hybrid nanoparticle was shown to generate ROS and consume ATP under near-infrared (NIR) light, transiently impairing P-gp function and creating a therapeutic window for chemotherapy [50,51]. Such multifaceted nano-formulations significantly increase drug accumulation in MDR tumor cells by inhibiting efflux pump activity at the protein or gene level.

3.2. Modulating the Tumor Microenvironment (TME)

The tumor microenvironment plays a critical role in MDR, contributing factors like hypoxia, dense extracellular matrix, and immunosuppressive cells (e.g. M2 tumor-associated macrophages, TAMs) [52]. Nanomedicine strategies increasingly target these components to reverse the supportive niche that fosters drug resistance. One approach is re-educating TAMs: delivering Toll-like receptor agonists or small interfering RNAs via nanoparticles can polarize macrophages from an M2 (pro-tumor, repair) phenotype to an M1 (pro-inflammatory, anti-tumor) phenotype [53]. This immunomodulation can heighten the tumor's response to therapy and reduce MDR, as M2-like TAMs are known to promote tumor growth and drug resistance [52]. Another strategy involves

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extracellular matrix (ECM) remodeling to improve drug penetration. Nanocarriers functionalized with enzymes like collagenase or hyaluronidase have been used to locally degrade collagen and hyaluronic acid in tumors. For instance, collagenase-decorated nanoparticles carrying DOX showed enhanced tissue penetration and reduced tumor fibrosis, thereby overcoming the ECM barrier to drug delivery [54]. As TME-driven immune evasions such as T and NK cell suppression in non-small cell lung cancer, contributes significantly to therapeutic failure[55], nanomedicine strategies that reprogram immunosuppressive niches offer a promising route to overcome such resistance. By modulating TME factors, normalizing abnormal vasculature, reducing interstitial pressure, re-polarizing macrophages, and enzymatically softening the stroma, nanotherapies can significantly improve the efficacy of chemotherapy in otherwise resistant tumors [52,56].

As summarized in Figure 1, multiple nanomedicine strategies have been developed to target key components of the tumor microenvironment, including TAM reprogramming, ECM remodeling, hypoxia-triggered drug release, and cytokine suppression.

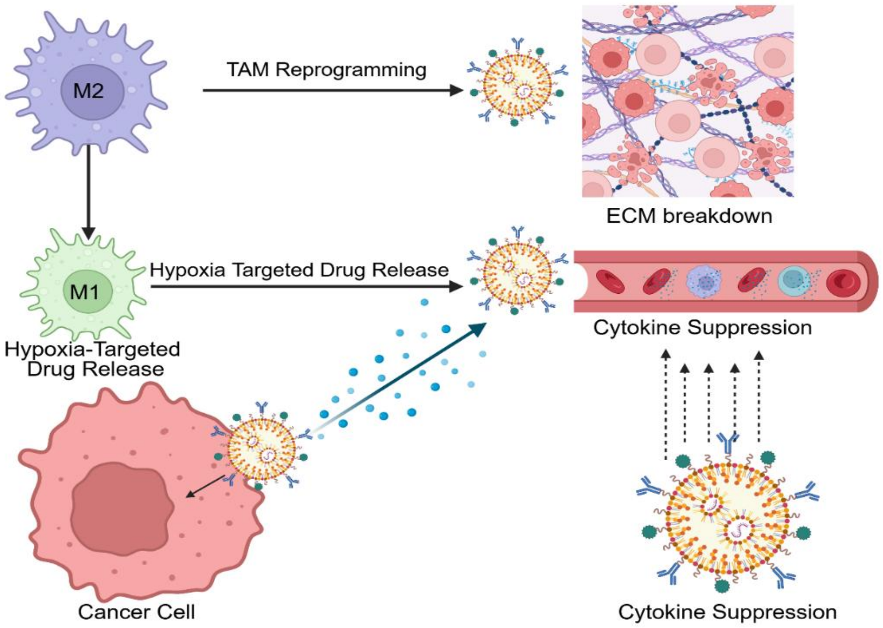

Figure 1. TME modulation via Nanoparticles.

3.3. Dual and Multi-Drug Co-Delivery Nanosystems

Co-delivery of multiple therapeutic agents in a single nanocarrier has emerged as a powerful method to tackle MDR. Advanced nanoparticles (liposomes, polymeric nanoparticles, dendrimers, etc.) can be engineered to carry two or more drugs simultaneously, allowing synergistic action and synchronized release. By incorporating a chemotherapeutic together with a chemosensitizer or a second drug, these nanosystems can attack cancer cells on multiple fronts. Key examples include:

3.3.1. Chemotherapy–chemosensitizer combination

Nanoparticles co-loaded with a conventional anticancer drug and an efflux pump inhibitor (e.g., DOX + tariquidar) or a reversal agent like verapamil have shown increased intracellular drug retention and cytotoxicity in resistant cell lines [57]. Similarly, the rational design of small-molecule chemotherapeutics, including benzofuran–piperazine derivatives with demonstrated cytotoxic activity, can complement nanocarrier-based delivery strategies by providing mechanistically potent payloads [58].

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3.3.2. Dual chemotherapies

Co-encapsulation of two chemotherapeutics that act via different mechanisms can produce synergistic killing. For instance, a cRGD-targeted lipid nanoparticle was developed to deliver gemcitabine and paclitaxel together, achieving enhanced breast cancer cell kill rates compared to either drug alone [59]. Such co-delivery ensures both drugs are present at the tumor in the optimal ratio and timing.

3.3.3. Drug–gene combinations

Nano-carriers can concurrently deliver a drug and a genetic therapy. Quantum-dot nanoconjugates have been reported that adsorb DOX together with siRNA targeting MDR genes; this approach successfully downregulated P-gp expression and resensitized cervical cancer cells (HeLa) to chemotherapy [60,61]. Similarly, mesoporous silica nanoparticles carrying DOX plus an siRNA against MDR1 gene achieved higher tumor inhibition in an MDR breast cancer model by blocking drug efflux at the gene level. Similarly, nanocarriers co-loaded with chemotherapeutics and immunostimulatory agents, such as IL-2, represent a promising strategy to simultaneously debulk tumors and enhance immune surveillance. Previous viral vector-based studies have demonstrated the feasibility and antitumor efficacy of IL-2-mediated immunotherapy in solid tumors [62].

Table 1. Examples of nano co-delivery systems overcoming MDR.

Nanoformulation	Drugs/Agents	Cancer Model	Key Outcomes (synergy)
Polymeric NP (mPEG-PLGA)	Paclitaxel dimer prodrug + Tetrandrine	MDR HeLa cells (cervical)	Enhanced uptake and ROS; ≈50% higher apoptosis vs. single drug
Polymeric NP (PEG-coated)	SN-38 (prodrug) + Ko143 (BCRP inhibitor)	BCRP-overexpressing CRC xenograft	Reversed irinotecan resistance; ~10-fold ↓ IC_{50}
Transferrin-PLGA NP	Gefitinib (EGFR-TKI) + Thymoquinone	Gefitinib-resistant NSCLC (A549/GR)	Re-sensitized to gefitinib; suppressed EMT (increased E-cadherin)
cRGD–Heparin NP	Cisplatin + Olaparib (PARP inhibitor)	Cisplatin-resistant ovarian	Inhibited P-gp/MRP2, ↑ DNA damage; overcame cisplatin resistance
Doxorubicin liposome + HCQ*	Doxorubicin + Hydroxychloroquine	DOX-resistant breast cancer	Restored apoptosis; polarized TAMs to M1 (↑TNFα, IL-12)

By tailoring nanocarrier release profiles and surface chemistry, dual-drug nanoparticles can ensure spatial and temporal co-localization of therapeutic agents in tumor cells, effectively bypassing mechanisms of resistance and yielding greater cytotoxic effect than single-drug treatments.

3.4. Tumor-Specific Targeting and Active Delivery Systems

To maximize drug delivery to cancer cells while sparing normal tissue, researchers are functionalizing nanocarriers with tumor-targeting ligands [63]. Such active targeting helps overcome MDR by strengthening the effective drug concentration at the tumor site. Common targeting moieties include transferrin (targets transferrin receptors often overexpressed in cancers), folic acid (targets folate receptors), antibodies or fragments (against tumor antigens), and peptides like cyclic RGD (cRGD) which bind integrin α_vβ_3 on tumor endothelium and cells [64,65].

Transferrin-conjugated nanoparticles are a prominent example: in one study, Tf-decorated PLGA nanoparticles loaded with an experimental organoselenium drug were tested against drug-resistant tumor cells. The Tf-NPs showed significantly higher cytotoxicity in P-gp overexpressing cancer cell lines compared to non-targeted NPs, indicating enhanced uptake via Tf receptor-mediated

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endocytosis [66,67]. In 3D tumor spheroid models of an MDR ovarian cancer line (NCI/ADR-RES), the Tf-NPs likewise penetrated better and reduced spheroid growth more effectively [68,69]. Similarly, cRGD functionalization of liposomes or polymeric NPs improves their accumulation in tumors by targeting neovasculature and invasive tumor cells. cRGD-modified nanoparticles were observed to undergo receptor-mediated endocytosis into α_vβ_3-expressing cancer cells, achieving higher intracellular drug delivery than untargeted particles [70,71]. In vivo imaging confirmed that cRGD-NPs concentrate preferentially in tumors, with reduced off-target distribution to liver and lungs [70].

Other ligand-targeted nanocarriers include folate-NPs (effective in folate receptor–positive ovarian and breast cancers), EGFR-targeted immunoliposomes, HER2-targeted nanoparticles for resistant breast cancer, and aptamer-guided NPs. By actively homing to tumor cells or the tumor microenvironment, these systems increase drug efficacy against MDR tumors and mitigate systemic toxicity [70,72]. The result is a higher therapeutic index and the ability to kill resistant cancer subpopulations that might evade passive delivery. Additionally, receptor-mediated delivery strategies are increasingly leveraged in nanoparticle design to enhance tumor targeting while minimizing off-target toxicity. For instance, receptor-based frameworks have been applied to bypass efflux-mediated resistance and improve intracellular drug retention [73].

3.5. Nanotechnology in Specific Cancers: Colorectal, Breast, Ovarian, and Kidney

Multi-drug resistance manifests differently across cancer types, and nanomedicine strategies have been tailored accordingly in colorectal, breast, ovarian, and kidney cancers:

3.5.1. Colorectal Cancer (CRC)

MDR in CRC (e.g., resistance to 5-fluorouracil or oxaliplatin) is often linked to efflux pumps and cancer stem cells. Nanocarriers have been explored to deliver combination therapies and siRNAs to overcome these mechanisms [74]. For instance, lipid nanoparticles co-loading 5-FU with curcumin (a natural chemosensitizer) have shown the ability to reverse 5-FU resistance in CRC cells [74,75]. Polymeric nanosystems targeting colon cancer stem cell markers are also under investigation to prevent recurrence and MDR. Early results demonstrate that nano-delivery can enhance drug uptake in CRC and downregulate survival pathways, improving chemosensitivity [74,75]. Additionally, preclinical studies such as those using CF10 polymer formulations have shown remarkable efficacy against colorectal cancer liver metastasis model, highlighting the translational potential of optimized nanopolymers[76–78] .

3.5.2. Breast Cancer

Breast tumors (especially triple-negative or recurrent tumors) commonly develop MDR through P-gp overexpression. Many studies use the doxorubicin-resistant MCF-7/ADR cell model to evaluate nano-therapies. Successful approaches include PEGylated liposomes carrying DOX plus P-gp inhibitors, and pH-responsive micelles delivering dual drugs [79,80]. A notable example combining DOX with siRNA against MDR1 in a pH-sensitive chitosan-based micelle, achieving dramatically higher tumor suppression in an MCF-7/ADR mouse model (87% tumor inhibition) compared to free DOX (~50%) [81,82]. Another approach used a hyaluronic-acid modified MoS_2 nanosheet to deliver DOX and perform photothermal therapy; under NIR laser, the nano-system generated heat and downregulated P-gp expression, leading to near-complete tumor ablation in an MDR breast cancer model [83–85]. These examples highlight that in breast cancer, nanomedicines can restore drug potency by both chemical and physical mechanisms (gene silencing, heat, etc.).

3.5.3. Ovarian Cancer

Ovarian tumors often exhibit MDR to platinum drugs and taxanes. Nanocarriers are being designed for intraperitoneal delivery in ovarian cancer to achieve high local drug levels. As

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mentioned, transferrin-targeted nanoparticles have shown promise in sensitizing ovarian cancer cells (like NCI/ADR-RES) to drugs [86]. Another strategy is delivering small molecule inhibitors of anti-apoptotic pathways (e.g., BCL-2 or PI3K/Akt) alongside chemo in a single nanoplatform [87–89]. In preclinical studies, dual-loaded NPs (e.g., paclitaxel + Akt siRNA) demonstrated the ability to overcome paclitaxel resistance in ovarian cancer xenografts by inducing apoptosis in otherwise refractory tumors [90–93]. Ongoing translational research in ovarian cancer focuses on nano-formulations of platinum drugs, PARP inhibitors, and gene therapies to bypass resistance and reduce systemic toxicity [94–96].

3.5.4. Kidney (Renal Cell) Cancer

Metastatic renal cell carcinoma (RCC) can develop resistance to targeted therapies like tyrosine kinase inhibitors (TKIs) [97]. Nanomedicine efforts here aim to deliver novel therapeutics or re-sensitize tumors to TKIs. One innovative example is the use of cuprous oxide (Cu_2O) nanoparticles to overcome resistance to sunitinib (a common RCC TKI) [98]. It is reported that Cu_2O NPs induce endoplasmic reticulum stress and ROS-mediated apoptosis in renal cancer cells, thereby restoring their sensitivity to sunitinib [99]. This nanoparticle effectively modulated copper trafficking inside tumor cells, pointing to a unique ferroptosis-like mechanism to kill drug-resistant RCC cells [100]. Additionally, dual-ligand liposomes targeting both RCC cells and angiogenic endothelium have shown promise in drug-resistant kidney tumors, by concentrating drugs in the tumor microvasculature and tumor tissue simultaneously [101]. While nanotherapy in kidney cancer is still nascent, these approaches suggest that overcoming resistance to targeted agents (like TKIs) is feasible with nanoparticle delivery that triggers alternative cell-death pathways or improved drug localization.

3.6. Emerging Strategies: Ferroptosis, Autophagy Modulation, Nitric Oxide, and Gene Therapy

Beyond conventional chemo, several cutting-edge approaches leverage nanotechnology to induce non-traditional cell death pathways or to modulate cellular survival mechanisms in MDR cancers:

3.6.1. Ferroptosis Induction

Ferroptosis is an iron-dependent form of programmed cell death characterized by lipid peroxidation. Recent studies highlight that inducing ferroptosis can help kill drug-resistant cancer cells that evade apoptosis [102]. Nanomedicines are being engineered as “ferroptosis nanoinducers” for example, ultrasmall iron oxide or magnetite nanoparticles that release Fe^{2+} to catalyze lipid ROS generation, or nanocarriers delivering ferroptosis-triggering drugs (like erastin or RSL3) [103]. The versatile ferroptosis-targeted nanotherapies have shown broad potential in reversing therapy resistance by directly triggering this pathway and by feedback regulation of cellular redox state [104]. In practice, combining ferroptosis inducers with chemo or immunotherapy (via co-loaded NPs) has yielded synergistic anti-tumor effects in refractory tumors, and is a hot area of preclinical research [105,106]. Additionally, targeting DNA repair checkpoints, such as CHK1 or PARP, offers another avenue to overcome resistance. CHK1 inhibition has been shown to potentiate DNA damage and sensitize chemoresistant ovarian tumors by modulating PARPylation and metabolic stress [107,108].

3.6.2. Autophagy Inhibition

Autophagy, a cellular recycling process, is a double-edged sword in cancer; in established tumors, moderate autophagy often promotes survival under therapeutic stress, contributing to MDR [109]. Thus, blocking cytoprotective autophagy can re-sensitize cancer cells to treatment. However, systemic autophagy inhibitors (like chloroquine derivatives) have off-target effects. Nanocarriers offer a way to target autophagy inhibitors to tumors. Researchers have loaded agents such as hydroxychloroquine (HCQ) or novel autophagy blockers into tumor-targeted nanoparticles to

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concentrate their action in tumor cells [110–112]. For example, Wuliji et al. formulated amphiphilic polymer micelles co-encapsulating HCQ and DOX; these NPs preferentially accumulated in tumors and effectively overcame DOX resistance by inhibiting autophagy flux in cancer cells [112]. Such nano-formulations ensure that autophagy is sufficiently inhibited in the tumor (preventing cancer cells from "recycling" damaged organelles and drugs) while minimizing toxicity elsewhere. Notably, some teams are also exploring autophagy activation in certain contexts (since excessive autophagy can induce cell death); both inhibition and promotion of autophagy via nanomedicines are being tested as strategies to collapse the defenses of MDR tumors [112–114].

3.6.3. Nitric Oxide (NO) Delivery

Nitric oxide is a gaseous signaling molecule that, at high concentrations, can kill cancer cells and modulate MDR pathways. NO has been found to downregulate P-glycoprotein expression and sensitize tumors to drugs. To exploit this, researchers have developed NO-releasing nanocarriers [115,116]. One innovative system is a supramolecular peptide hydrogel loaded with a NO prodrug and DOX: when injected into a tumor, the hydrogel slowly releases NO (especially in the presence of high glutathione levels in the TME) alongside DOX [117,118]. The burst of NO not only directly damages tumor cells via oxidative stress, but also reverses P-gp–mediated MDR, making cancer cells more susceptible to DOX [119]. In vivo studies in MDR breast cancer models showed that this NO-releasing co-delivery platform significantly enhanced tumor shrinkage compared to DOX alone [120]. Another study encapsulated an NO donor and camptothecin in a PLGA nanoparticle; under the acidic conditions of the tumor, NO was generated, which destabilized the NP and triggered drug release in situ. The released NO reduced P-gp levels by ~45%, thereby permitting a much higher intracellular concentration of camptothecin [121]. These results underscore NO's potential as a chemosensitizing agent when delivered via a controlled nanocarrier.

3.6.4. Gene Therapy and RNA Interference

Nanotechnology enables gene-based therapies to overcome MDR, such as siRNA, shRNA, mRNA or CRISPR/Cas9 systems directed against resistance-related genes [122]. Because nucleic acids alone have poor stability and delivery, nano-formulations (lipid nanoparticles, polymeric polyplexes, etc.) are essential for their clinical use [123,124]. Numerous studies have shown that siRNA against MDR1 (ABCB1) delivered by nanoparticles can knock down P-gp expression and restore drug sensitivity in vitro and in vivo [125–127]. For example, a hierarchical mesoporous silica nanocarrier was used to co-deliver DOX plus an anti-Pgp siRNA: the MSN protected the siRNA from degradation and released both payloads inside multidrug-resistant breast cancer cells, leading to P-gp silencing and significantly higher chemotherapy efficacy [128]. Beyond P-gp, researchers are targeting other resistance genes (BCL-2, Akt, MYC, etc.) using siRNA or even CRISPR delivered by viral-mimicking nanoparticles [129]. Similarly, modulation of oncogenic miRNAs like miR-221-5p has been implicated in chemoresistance, further justifying nanoparticle-mediated miRNA therapies in resistant ovarian cancers [130]. The upregulation of lymphoblastic leukemia-derived sequence-1 (LYL1) has been implicated in the progression and metastatic potential of ovarian cancer, highlighting it as a potential target for gene-silencing approaches. Sah et al. demonstrated the oncogenic role of LYL1 in ovarian cancer models, supporting the rationale for RNAi-loaded nanocarriers designed to reverse oncogene-driven drug resistance [131]. Early results are promising, showing that silencing or editing genes can directly reverse MDR phenotypes. However, gene therapy approaches must surmount delivery challenges and potential off-target effects and thus are often combined with nanoparticle strategies for tumor-specific, controlled delivery [132,133].

In summary, these emerging nano-strategies aim to attack MDR cancer cells via novel mechanisms inducing ferroptotic cell death, shutting down autophagy survival pathways, using bioactive gases like NO, or reprogramming gene expression – thereby supplementing conventional cytotoxic drugs and overcoming resistance that arises from classic mechanisms.

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3.7. *Stimuli-Responsive Nanotherapies: Ultrasound, Photothermal, and Sonodynamic Approaches*

Stimuli-responsive nanomedicine adds another layer of innovation to combat MDR by using external triggers (such as light or sound) to activate drug delivery or kill tumor cells by non-chemical means [134,135]. These approaches can bypass drug efflux and damage resistant cells through physical mechanisms:

3.7.1. Photothermal Therapy (PTT)

This involves nanoparticles that absorb NIR laser light and convert it to heat, selectively killing cancer cells or disrupting their membranes. Photothermal agents (gold nanoshells, nanorods, carbon nanomaterials, graphene oxide, etc.) can be loaded with chemotherapeutics for a combined effect. Under NIR irradiation, the localized heating can enhance drug release from the nanocarrier and also sensitize tumor cells (e.g., by causing protein denaturation or ATP depletion) [136–138]. PTT has been shown to downregulate efflux pumps: for example, mild hyperthermia (≈52°C) generated by MoS_2 nanosheets caused a significant reduction in P-gp levels in MDR breast cancer cells [139,140]. In one study, PLGA nanoparticles co-loaded with DOX and indocyanine green (ICG, an FDA-approved NIR dye) were used to treat MCF-7/ADR tumors. NIR laser exposure of these NP in tumors led to heat generation (from ICG) and triggered DOX release; the combination of chemotherapy + PTT effectively destroyed drug-resistant breast cancer cells in vitro and in vivo [141]. Photothermal nano-therapy thus provides a way to physically eradicate cancer cells that might survive chemical therapy, and when integrated with drug delivery, it produces a synergistic anti-MDR effect.

3.7.2. Ultrasound and Sonodynamic Therapy (SDT)

Ultrasound can penetrate deep into tissues and be focused on tumor sites, making it a valuable trigger for drug release or activation of sonosensitizers [142,143]. In SDT, a sonosensitizer compound (often a porphyrin, IR780, or other ROS-generating molecule) is delivered by a nanoparticle and produces cytotoxic reactive oxygen species when exposed to low-intensity ultrasound. This strategy is particularly useful against hypoxic or deep-seated MDR tumors [144,145]. A recent breakthrough involved cRGD-targeted gold nanoparticles loaded with the EGFR inhibitor gefitinib and the sonosensitizer IR780 [146]. The gold shell provided a photothermal effect (for on-demand drug release) and IR780 generated ROS under ultrasound; together, this low-temperature PTT + SDT combination was able to overcome acquired TKI resistance in an EGFR-mutant NSCLC model [146]. The ultrasound-triggered ROS helped kill cancer cells independent of drug action, while also impairing cellular defense mechanisms, and the mild heating facilitated drug uptake [147,148]. Beyond this, ultrasound is also used to trigger drug release from acoustically responsive nanocarriers (like liposomes or microbubbles) at the tumor site, ensuring a high local drug concentration that can overwhelm efflux pumps [149,150]. Sonodynamic and ultrasound-triggered therapies are still in translational stages, but they exhibit tremendous potential to non-invasively eliminate MDR cancer cells and can be repeated or spatially controlled with imaging guidance (many ultrasound-sensitive NPs also serve as contrast agents) [151].

3.7.3. Other External Triggers

Magnetic field–responsive nanoparticles (e.g., iron oxide NP for magnetic hyperthermia or drug targeting), photodynamic therapy (light-activated generation of singlet oxygen using NP-delivered photosensitizers), and radiation-triggered nanoparticle release are additional modalities under exploration [152,153]. For instance, magnetically heated nanoparticles or X-ray-activated liposomes could help in circumventing resistance by causing direct tumor cell damage or by releasing drugs in a burst when the tumor vasculature is most permeable. These methods, often termed “externally responsive nanotherapies,” can be combined with chemotherapy to potentiate treatment effects [154]. By carefully tuning the stimulus (laser wavelength, ultrasound frequency, magnetic field strength),

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clinicians can activate the nanoparticle only at the tumor site, thereby achieving high precision [154,155].

In summary, stimuli-responsive nanotherapies offer a way to attack MDR tumors using physical forces (heat, sound, light) that cancer cells are less equipped to resist. When coupled with smart nanocarriers, these approaches release drugs at the optimal time or bypass biochemical resistance entirely, and they have demonstrated impressive results in preclinical MDR cancer models [156]. To illustrate the diversity and mechanisms of nanocarrier-based co-delivery systems that successfully circumvent MDR in different cancers, a schematic representation of selected strategies is shown in Figure 2, corresponding to the formulations detailed in Table 2.

Table 2. Stimuli-responsive nanotherapy modalities for MDR cancer.

Stimulus	Mechanism (effects)	Representative Cancer Model/Type
Ultrasound (US)/SDT	Cavitation increases drug uptake; triggers ROS from sonosensitizers (deep penetration)	Pancreatic cancer, breast cancer, brain (glioblastoma)
Photothermal (PTT)	NIR light → nanoparticle heats tumor (45–60°C), causing protein denaturation and cell death (efflux-independent)	Skin, head/neck, breast tumors (where NIR penetrates)
Chemophotodynamic (PDT)	Light activates photosensitizer → ROS (singlet O_2); synergizes with chemo	Superficial tumors, MDR melanoma models
Sonodynamic (US + sensitizer)	Ultrasound activates sensitizer → ROS; deep-tissue effect	Deep tumors (brain, pancreas)
Hyperthermia	Elevated temperature triggers drug release (thermosensitive liposomes) and tumor cell death	Liver (HCC), prostate

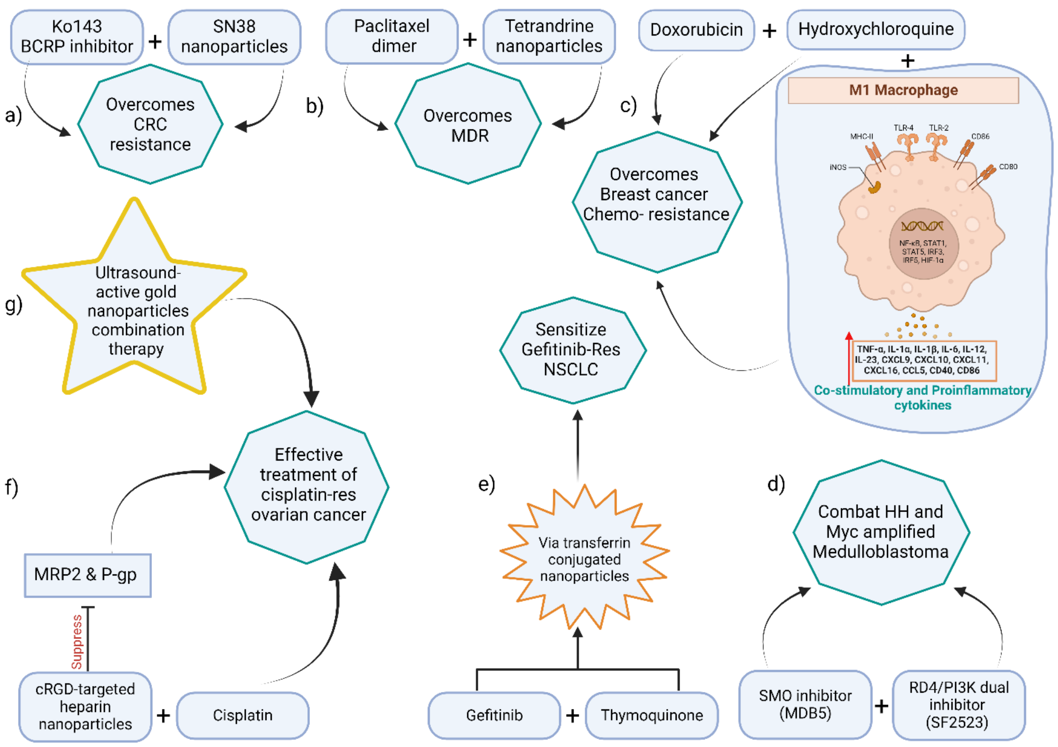

Figure 2. Mechanistic Pathways of Nanomedicine Co-Delivery Platforms Targeting Multidrug Resistance Across Diverse Cancer Types.

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3.8. Innovative and Underexplored Nanomedicine Strategies for MDR Cancers

While significant attention has been given to co-delivery systems, tumor microenvironment modulation, and stimuli-responsive release strategies, recent studies have spotlighted a new wave of highly promising nanomedicine innovations. These approaches, while underrepresented in earlier clinical trials, are gaining traction for their ability to circumvent traditional resistance mechanisms through novel physicochemical properties and delivery modalities.

3.8.1. Magnetic Nanoparticles for Theranostics and Targeted Therapy

Magnetic nanoparticles (MNPs), particularly superparamagnetic iron oxide nanoparticles (SPIONs), offer dual functionality as both therapeutic and diagnostic agents [157]. When guided by an external magnetic field, MNPs can accumulate at the tumor site with high specificity, allowing for concentrated drug delivery [158]. Moreover, magnetic hyperthermia where MNPs generate localized heat in response to an alternating magnetic field has demonstrated synergy with chemotherapeutics and the capacity to downregulate drug efflux pumps like P-gp [159]. This form of image-guided, magnetically targeted therapy is especially promising for difficult-to-treat or deep-seated tumors.

3.8.2. Intratumoral Administration of Nano Drug Delivery Systems

Intratumoral injection of nano-formulations bypasses systemic pharmacokinetic barriers and delivers high drug concentrations directly into tumor tissue [160]. This strategy enhances local therapeutic efficacy while reducing off-target toxicity. Various delivery systems such as hydrogels, polymeric micelles, and dendritic nanogels have been engineered for sustained and localized drug release following intratumoral injections. This modality is particularly effective in poorly vascularized or desmoplastic tumors, where systemic delivery fails to achieve adequate penetration [161,162].

3.8.3. Polydopamine (PDA) Nanoparticles in Drug Delivery and Immune Modulation

Polydopamine-based nanoparticles exhibit excellent biocompatibility, surface adhesion, and responsiveness to oxidative environments [163]. PDA nanocarriers have been to provide immune modulation, photothermal effect and chemotherapeutic effect simultaneously. [164]. These nanoparticles generate heat when exposed to near-infrared light which can damage cancer cell membranes or sensitize resistant cells to chemotherapy [165]. Additionally, PDA systems have shown promise in modulating immune responses by carrying Toll-like receptor agonists or checkpoint inhibitors, thus bridging drug delivery with tumor immunotherapy [166].

3.8.4. Inorganic Nanoparticles in Overcoming Resistance

Inorganic nanomaterials, including gold nanoparticles, mesoporous silica, and quantum dots offer unique optical, electrical, and structural features [167]. These carriers are not only effective in delivering therapeutics but also enhance imaging and diagnosis. Several studies have demonstrated that inorganic NPs can induce ROS generation, promote apoptosis, and even directly interfere with intracellular resistance pathways [168–170]. Quantum-dot conjugates, for instance, allow real-time tracking while co-delivering siRNA and chemotherapeutic agents to downregulate MDR-associated genes [171,172].

3.8.5. Oral Nanoformulations for Colorectal Cancer

Oral administration of nanomedicine is particularly valuable in colorectal cancer therapy [173]. Engineered nanoparticles with pH-sensitive or mucoadhesive properties can bypass gastric degradation and release drugs specifically in the colon [174,175]. Co-formulations combining 5-FU with natural chemosensitizers like curcumin have shown enhanced drug retention and MDR reversal [176]. These systems offer improved patient compliance and the potential to deliver both cytotoxic

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and immunomodulatory agents directly to the tumor site, which is crucial in colorectal tumors with localized resistance profiles [177].

Together, these underexplored strategies highlight the evolving landscape of nanomedicine for drug-resistant cancers. Their distinct mechanisms ranging from magnetic targeting and localized hyperthermia to oxidative disruption and site-specific oral delivery complement established approaches and provide new opportunities to overcome therapeutic resistance in challenging cancer subtypes.

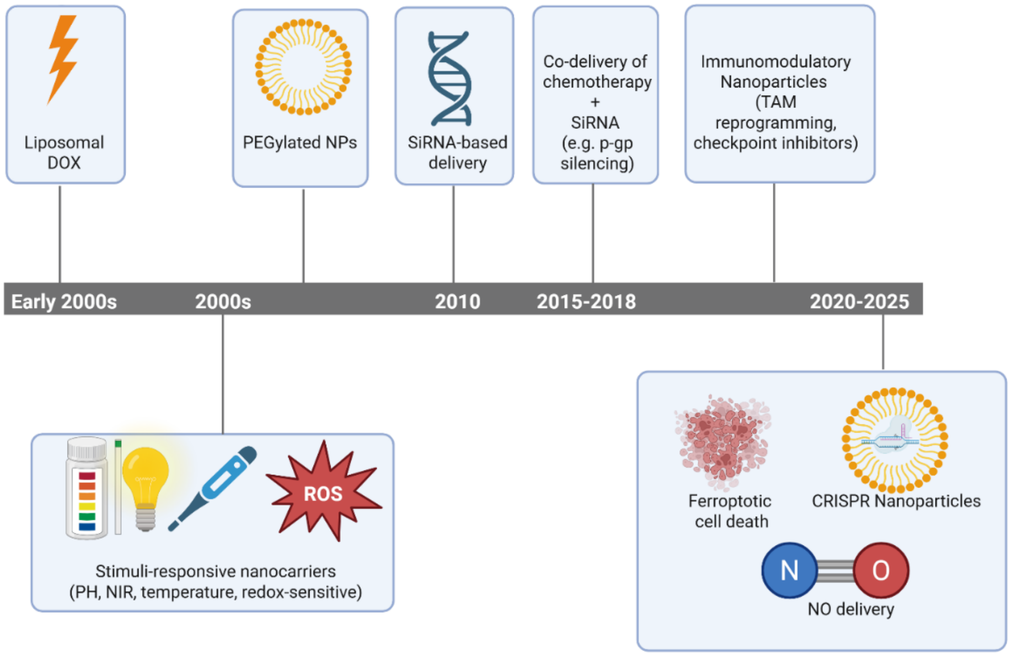

Figure 3. The Historical development of nanomedicine platforms aimed at reversing MDR, highlighting the evolution from conventional liposomal drugs to gene-editing and ferroptosis-inducing nanocarriers.

4. Clinical Translation: Limitations and Challenges

Despite the plethora of promising nanomedicine strategies in preclinical studies, translating these innovations into clinical use faces significant challenges. The first consideration is the complexity of regulatory approval for nanodrugs. Nanomedicines often don't fit neatly into existing regulatory categories, they may be classified as drugs, biologics, devices, or combination products, which complicates the approval pathway [178]. Regulatory agencies like the FDA and EMA have been cautious, requiring extensive characterization of nanoparticle physicochemical properties, manufacturing consistency, and toxicity profiles. Key hurdles include:

4.1. Sandardization and Characterization:

There is a lack of standardized guidelines specific to nanomedicines [178]. Small variations in formulation (particle size, surface charge, etc.) can dramatically alter a nanoparticle's behavior in vivo [179]. Thus, companies must implement advanced analytical techniques and strict quality controls to ensure batch-to-batch consistency and well-characterized products [178,180]. Demonstrating reproducibility and stability of complex nanoparticle formulations (which may comprise multiple components like polymers, lipids, targeting ligands, and drugs) is much more involved than for small-molecule drugs. This also affects the development of "nanosimilars" (generic versions of nanodrugs), where establishing equivalence is non-trivial [180,181].

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4.2. Safety and Toxicity Concerns

While nanocarriers can reduce the systemic toxicity of potent drugs, the long-term fate of nanoparticles in the body is not fully understood. Issues such as accumulation in the reticuloendothelial system (liver, spleen), unforeseen immunogenic reactions, or off-target effects of the nanoparticle components must be addressed [182]. Extensive preclinical studies are needed to evaluate biocompatibility, for example, whether the NP triggers complement activation or how it is excreted or metabolized [183]. Some high-profile nanodrugs have failed in trials due to toxicity or immune-related adverse events not predicted by animal models [184,185]. Rare but severe immune-mediated reactions to pharmacological agents, such as sulfasalazine-induced DRESS syndrome, underscore the importance of vigilant safety profiling and post-marketing surveillance in both traditional and nanomedicine therapies [186]. In addition to manufacturing and scalability, successful integration of nanomedicine into real-world clinical settings requires alignment with hospital practices, prescriber behaviors, and resource availability. System-level challenges, such as noncompliance with prescription-writing standards, delayed IV-to-oral transitions, and inconsistent infection management protocols highlight the barriers to adopting complex therapeutic innovations like nanomedicine in routine care [187–189]. Moreover, including pharmacists in clinical audit workflows has shown to improve adherence to treatment protocols and could support future implementation of nanomedicine [190]. Overcoming MDR in a tumor is controversial if nanotherapy cannot be used safely in patients, so ensuring safety profiles and conducting rigorous toxicity studies (including looking at chronic exposure) is essential [191,192].

4.3. Manufacturing and Scalability

Producing nanomedicines at a commercial scale with uniform quality is challenging [193]. Techniques used in the lab (like microfluidic mixing or small-batch emulsification) may not easily translate to industrial scale. Additionally, sterile filtering or validating complex nanoconjugates can be difficult [194]. Scaling up often requires significant engineering and process development, and any process changes might alter the NP properties, sending developers back to perform comparability studies [195]. For example, standardized methods for the growth, purification, and titration of virus-based therapies, such as oncolytic herpes simplex viruses, have been developed to improve process reproducibility and safety, offering insights applicable to viral and gene-based nanocarriers [196]. Scaling up contributes to the high cost of bringing nanodrugs to the market [197]. Manufacturing complexities also tie into regulatory hurdles, as changes in a nanomedicine's production may trigger the need for new safety evaluations [198,199].

4.4. Efficacy in Human Tumors

A well-known challenge in cancer nanomedicine is the gap between preclinical efficacy (often in mouse xenograft models) and clinical efficacy in human patients [200]. The enhanced permeability and retention (EPR) effect, which allows nanoparticles to accumulate in tumors due to leaky vasculature, is variable in humans – many human tumors have irregular blood supply or higher interstitial pressure that limits nanoparticle penetration [201,202]. Consequently, some nanoparticles that work in mice don't achieve sufficient tumor delivery in patients [203]. Heterogeneity among patients and tumor types means that nanomedicines might benefit some patients more than others [204]. For clinical translation, better methods to image and verify NP delivery in human tumors are needed (e.g., PET or MRI-labeled nanoparticles) to select patients most likely to benefit [204].

4.5. Economic and Practical Considerations

The cost of developing and producing nanomedicines can be substantially higher than for traditional drugs [205]. This includes the cost of specialized facilities and analytical assays. These costs can make nanodrugs expensive, potentially limiting patient access or insurance acceptance [206]. Additionally, regulatory approval times can be longer due to the need for expert consultations

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on nanotech aspects [207]. From a practical standpoint, the shelf-life and storage conditions of nanomedicines (some may require cold storage or have shorter stability) can be a logistical challenge for distribution [208,209]. Real-world implementation of nanomedicine must also account for disparities in patient comprehension, as limited health literacy has been shown to hinder cancer care engagement and decision-making in vulnerable populations [210].

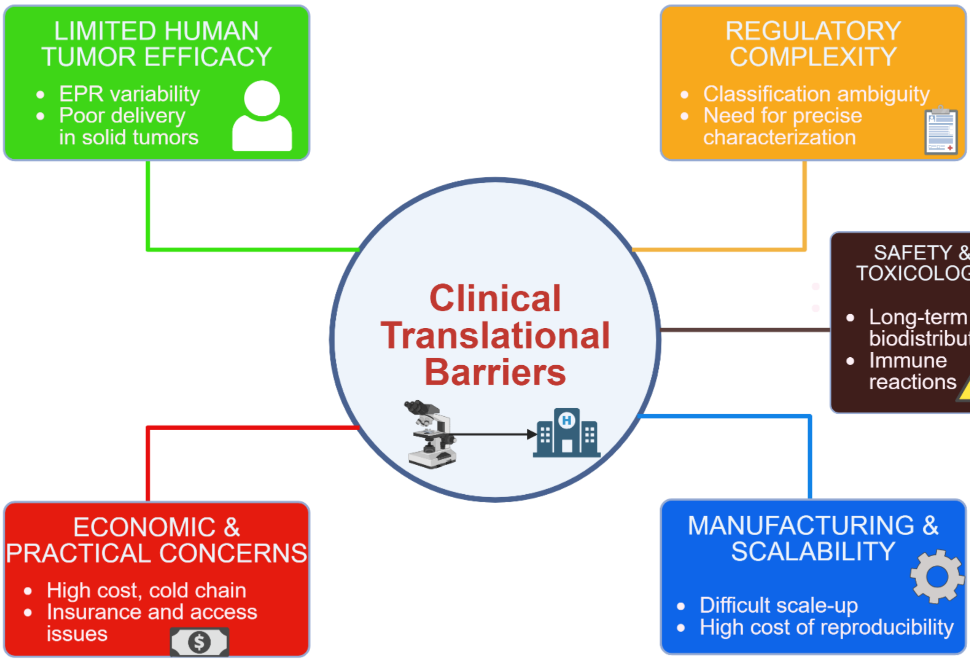

Figure 4. Key challenges in the clinical translation of nanomedicine for multidrug-resistant (MDR) cancers. The schematic summarizes five major hurdles: (1) regulatory complexity due to overlapping classification and lack of standardization; (2) safety and toxicity concerns including unpredictable biodistribution and immune responses; (3) manufacturing and scalability issues affecting reproducibility and cost; (4) limited clinical efficacy stemming from tumor heterogeneity and variable nanoparticle delivery; and (5) economic and logistical barriers related to high production costs, cold chain requirements, and limited accessibility. Addressing these interconnected limitations is essential for successful bench-to-bedside translation.

Despite these challenges, progress is being made. A growing number of nanomedicines have achieved clinical approval (including many liposomal drugs, polymer–drug conjugates, and nanoparticle-albumin-bound drugs), proving that regulatory and manufacturing hurdles are surmountable [211]. As of mid-2025, over 100 nanotechnology-based therapeutics or diagnostics have been approved for clinical use [212], though most are reformulations of existing drugs rather than novel MDR-targeting systems [213]. Importantly, lessons from these successes are informing next-generation designs: for instance, using biodegradable materials to improve safety, simplifying nanoparticle compositions to ease manufacturing, and developing clear regulatory standards [214]. Collaborations between academia, industry, and regulatory bodies are ongoing to refine guidelines specific to nanomedicine [215]. In parallel, clinical trial designs are adapting, sometimes incorporating patient stratification (e.g., selecting patients with leaky tumors or certain biomarkers for nanoparticle uptake) to demonstrate benefit [216,217].

5. Conclusions

In conclusion, while nanomedicine offers innovative solutions to overcome cancer MDR – through targeted delivery, co-therapy, microenvironment modulation, and externally-triggered release – the journey from bench to bedside requires careful navigation of regulatory, safety, and

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production challenges. Ongoing innovations and a better understanding of how nanoparticles behave in patients will help ensure that the most promising laboratory breakthroughs can be translated into real-world cancer therapies [218]. The continued success of nanomedicine in the clinic will pave the way for these multi-modal MDR-reversing strategies to become part of standard cancer care in the future.

Author Contributions: For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used "Conceptualization, S.K.Y., V.B.C., K.B.R.; methodology, S.K.Y., V.B.C., K.B.R.; software, N.U.P., M.S.D.; validation, N.U.P., M.S.D., K.B.R.; formal analysis, M.S.D., K.B.R.; investigation, N.U.P., M.S.D., K.B.R.; resources, N.U.P., M.S.D., K.B.R.; data curation, S.K.Y., V.B.C.; writing—original draft preparation, S.K.Y., V.B.C.; writing—review and editing, N.U.P., M.S.D., K.B.R.; visualization, N.U.P., M.S.D.; supervision, N.U.P., M.S.D., K.B.R.; project administration, N.U.P., M.S.D., K.B.R.; funding acquisition, S.K.Y., K.B.R.

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