# Multifunctional Nanoparticles to Over Come ABC Transporter-Mediated Drug Resistance in Cancer: A Short Review

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***Abstract*****—***Multidrug resistance mediated by ATP-binding cassette transporters remains a critical barrier to effective cancer chemotherapy, driving tumor recurrence and treatment failure. This review comprehensively examines innovative multifunctional nanoparticle strategies designed to overcome transporter-mediated efflux mechanisms. We analyze nanocarrier platforms enabling targeted co-delivery of chemotherapeutics with transporter inhibitors, gene-silencing approaches suppressing efflux pump expression, and stimuli-responsive systems exploiting tumor microenvironment features. The work highlights emerging technologies including nanobots and AI-designed nanoparticles while addressing translational challenges like protein corona formation and manufacturing scalability. By synthesizing recent advances in nanomedicine, this review provides researchers with critical insights into next-generation approaches for combating drug-resistant cancers through rational nanomaterial engineering.*

***Keywords— nanocarrier systems; nanomedicine; Cancer nanotherapeutics; Multidrug resistance reversal; ABC transporters***

## I. INTRODUCTION

Cancer remains a formidable global health challenge and a leading cause of mortality worldwide [1]. While chemotherapy is a cornerstone of systemic cancer treatment, its efficacy is frequently undermined by the development of multidrug resistance (MDR), a phenomenon where cancer cells become simultaneously insensitive to a broad spectrum of structurally and functionally distinct anticancer drugs [2]. MDR is a primary factor in the failure of many chemotherapeutic regimens, leading to tumor recurrence and patient relapse. A principal mechanism responsible for mediating this resistance is the overexpression of ATP-binding cassette (ABC) transporters in cancer cells [3], [4]. These membrane-bound proteins function as energy-dependent efflux pumps, actively expelling a wide range of chemotherapeutic agents from the intracellular environment, thereby reducing their cytosolic concentration and preventing them from reaching their therapeutic targets [5].

Overcoming ABC transporter-mediated MDR is therefore a critical objective in oncology research. Traditional approaches, such as the co-administration of small-molecule inhibitors of ABC transporters, have been met with limited success, often due to systemic toxicity and unfavorable pharmacokinetic profiles [6]. In recent years, the convergence of nanotechnology and medicine has offered a paradigm-shifting approach to address this challenge. Multifunctional nanoparticles have emerged as a highly promising platform for circumventing MDR, owing to their unique physicochemical properties and their capacity for sophisticated molecular engineering [7]. These nanoscale delivery systems can be designed to encapsulate therapeutic payloads, protecting them from premature degradation and recognition by efflux pumps. Furthermore, their surfaces can be modified with targeting ligands for specific delivery to tumor cells and with agents that can actively inhibit ABC transporter function or deplete the cellular energy required for drug efflux.

This review aims to provide a comprehensive and critical analysis of the state-of-the-art strategies employing multifunctional nanoparticles to overcome ABC transporter-mediated drug resistance in cancer. We will systematically survey the various types of nanocarriers investigated, including liposomes, polymeric nanoparticles, and inorganic nanoparticles, and detail the diverse mechanisms through which they bypass or suppress efflux pump activity. The discussion will encompass passive and active targeting strategies, co-delivery of chemotherapeutics with ABC transporter inhibitors, and innovative approaches designed to modulate the tumor microenvironment to enhance drug efficacy.

The significance of this review lies in its synthesis of recent advancements in a rapidly evolving and clinically significant

field. By elucidating the design principles, mechanisms of action, and therapeutic potential of multifunctional nanoparticles, we aim to provide a valuable resource for researchers in oncology, pharmacology, and materials science. Ultimately, a deeper understanding of these sophisticated nanomedical strategies will be instrumental in guiding the rational design of next-generation therapies capable of conquering drug resistance and improving clinical outcomes for cancer patients.

## II. ABC TRANSPORTERS: MECHANISMS AND THERAPEUTIC CHALLENGES

The ATP-binding cassette (ABC) transporter superfamily represents one of the largest families of transmembrane proteins, playing indispensable roles in cellular homeostasis by facilitating the transport of a vast array of substrates across biological membranes [8]. While essential for physiological processes, a subset of these transporters, notably P-glycoprotein (P-gp, or ABCB1), breast cancer resistance protein (BCRP, or ABCG2), and multidrug resistance-associated protein 1 (MRP1, or ABCC1), are key drivers of multidrug resistance (MDR) in oncology [9], [10], [11]. Their ability to recognize and actively extrude a wide spectrum of chemotherapeutic agents from cancer cells constitutes a formidable barrier to effective treatment. Understanding the intricate structural mechanics of these efflux pumps and the historical context of their therapeutic inhibition is crucial for developing strategies to overcome the clinical challenge of MDR.

The clinical relevance and complexity of this superfamily are underscored by the sheer number of transporters implicated in cancer resistance, the broad range of affected malignancies, and the extensive list of chemotherapeutic drugs they can expel, as detailed in Table 1. Beyond the well-studied P-gp, BCRP, and MRP1, other members of the ABCB, ABCC, and ABCG subfamilies are also significantly involved in conferring drug resistance across various cancer types. For example, MRP2 (ABCC2) contributes to resistance in hepatocellular carcinoma [12], while MRP7 (ABCC10) has been shown to transport taxanes, implicating it in resistance in ovarian and breast cancers [13], [14]. Table 1 illustrates a critical challenge for clinicians: a single tumor type, such as breast cancer, can co-express multiple distinct efflux pumps (e.g., P-gp, BCRP, MRP1), creating a redundant and highly robust resistance network [13]. Furthermore, the substrate polyspecificity is extensive; a single drug like doxorubicin is a substrate for at least P-gp and MRP1 [15], while a single transporter like P-gp can efflux a chemically diverse arsenal of drugs including taxanes, vinca alkaloids, and anthracyclines [16], [17]. This vast functional overlap and redundancy highlight the inherent limitations of targeting a single transporter and form the rationale for developing strategies that can circumvent these efflux mechanisms altogether.

TABLE I. CLINICALLY RELEVANT MAJOR ABC TRANSPORTERS, ASSOCIATED MALIGNANCIES, AND CHEMOTHERAPEUTIC SUBSTRATES.

| ABC Transporter | Alternative Names | Associated Cancers | Substrate Drugs | References |
|---|---|---|---|---|
| ABCB1 | P-glycoprotein (P-gp), MDR1 | Breast cancer, Ovarian cancer, Melanoma, Hepatocellular carcinoma, Acute myeloid leukemia, Chronic myeloid leukemia, Prostate cancer, Triple-negative breast cancer | Doxorubicin, Paclitaxel, Vincristine, Vinblastine, Etoposide, Cisplatin, Docetaxel, Imatinib, Tamoxifen, Vemurafenib, Olaparib, Daunorubicin, Mitoxantrone, Topotecan, Rhodamine 123 | [18], [19], [20], [21], [22], [23], [24], [25], [26], [27], [28], [29], [30] |
| ABCC1 | MRP1 (Multidrug Resistance-associated Protein 1) | Breast cancer, Melanoma, Hepatocellular carcinoma, Lung cancer, Ovarian cancer | Doxorubicin, Vincristine, Etoposide, Methotrexate, Cisplatin, Gemtuzumab ozogamicin | [31], [32], [33], [34] |
| ABCG2 | BCRP (Breast Cancer Resistance Protein) | Breast cancer, Non-small cell lung cancer, Melanoma, Hepatocellular carcinoma, Ovarian cancer | Imatinib, Topotecan, Sorafenib, Sunitinib, Gefitinib, Mitoxantrone, Doxorubicin, Photodynamic therapy agents | [35], [36], [37], [38], [39], [40], [41] |
| ABCC2 | MRP2 | Melanoma, Hepatocellular carcinoma | Cisplatin, Sorafenib | [32], [42] |
| ABCC3 | MRP3 | Paclitaxel-resistant breast cancer, Non-small cell lung cancer | Doxorubicin, Paclitaxel-OregonGreen488 | [43] |
| ABCC4 | MRP4 | Melanoma, Hepatocellular carcinoma | Doxorubicin, Cisplatin | [31], [32] |
| ABCC5 | MRP5 | Paclitaxel-resistant breast cancer, Non-small cell lung cancer | Doxorubicin, Paclitaxel-OregonGreen488 | [43] |
| ABCC9 | MRP9, SUR2 | Hepatocellular carcinoma, Melanoma | Various chemotherapeutics | [31], [32] |
| ABCC10 | MRP7 | Paclitaxel-resistant breast cancer, Non-small cell lung cancer | Doxorubicin, Paclitaxel-OregonGreen488 | [43] |
| ABCG1 | - | Melanoma, Hepatocellular carcinoma | Various chemotherapeutics | [31], [32] |
| ABCB8 | - | Melanoma | Cisplatin | [31], [32] |
| ABCA1 | - | Breast cancer | Various chemotherapeutics | [44] |

The functional core of an ABC transporter lies in its unique architecture, which consists of two nucleotide-binding domains (NBDs) and two transmembrane domains (TMDs). The NBDs, located in the cytoplasm, are responsible for binding and hydrolyzing ATP, providing the energetic force for transport. The TMDs, each typically composed of six alpha-helices, form a central translocation pathway and confer substrate specificity [45]. Seminal work

in structural biology, particularly through cryo-electron microscopy (cryo-EM), has revealed the dynamic, ATP-dependent conformational cycle that powers substrate efflux [46], [47]. In its resting state, the transporter adopts an inward-facing conformation, allowing substrates to enter the central cavity from the cytoplasm or the inner leaflet of the cell membrane. Upon substrate binding, followed by ATP binding to the NBDs, the transporter undergoes a dramatic conformational rearrangement to an outward-facing state. This "power stroke" expels the substrate into the extracellular space. Subsequent ATP hydrolysis and phosphate release reset the transporter back to its inward-facing conformation, completing the cycle and preparing it for another round of efflux. While this general model is widely accepted, a significant gap in our knowledge remains regarding the precise molecular determinants of the remarkable polyspecificity of transporters like P-gp, which can recognize hundreds of chemically diverse compounds. The structural basis for this promiscuous binding remains an area of intense investigation, with current hypotheses suggesting a large, flexible, and chemically heterogeneous binding pocket [48].

The direct inhibition of ABC transporters emerged as a logical and promising strategy to reverse MDR. The initial "first generation" of inhibitors comprised repurposed drugs that were incidentally found to have inhibitory activity against P-gp, such as the calcium channel blocker verapamil and the immunosuppressant cyclosporine A [49], [50], [51]. Early *in vitro* studies were highly encouraging, demonstrating a restoration of chemosensitivity in resistant cell lines. However, these promising preclinical results failed to translate into clinical success. The fundamental limitation of these first-generation inhibitors was their low potency and lack of specificity. The high concentrations required to achieve effective P-gp inhibition in patients resulted in significant dose-limiting toxicities related to their primary pharmacological actions. For instance, the use of verapamil was severely hampered by cardiovascular side effects, making its clinical application untenable [52].

These initial failures spurred the development of "second and third-generation" inhibitors, which were specifically designed for high-potency and high-specificity inhibition of ABC transporters, devoid of other pharmacological activities. Agents like PSC 833 (valspodar) and tariquidar showed substantially improved potency in preclinical models [53], [54]. Despite this, they too encountered significant hurdles in clinical trials. A major issue was the unpredictable and complex pharmacokinetic interactions with co-administered chemotherapeutic agents, as many inhibitors also affect drug-metabolizing enzymes like cytochrome P450 [55]. Furthermore, even potent inhibitors failed to produce the expected dramatic improvements in patient outcomes. This has led to a critical re-evaluation of the strategy, with a growing consensus that complete inhibition of a single transporter may be insufficient to overcome the multifactorial nature of drug resistance. Cancer cells often co-express multiple ABC transporters, and blocking one may simply be compensated for by others. The inherent heterogeneity of tumors, where transporter expression can vary significantly between cells, further complicates this approach. Therefore, while the pursuit of potent and specific inhibitors continues, future research must also focus on developing strategies that are less susceptible to these compensatory mechanisms, such as nanoparticle-based delivery systems that can bypass efflux pumps entirely or novel agents that modulate transporter expression at the genetic level.

## III. NANOCARRIER DESIGN STRATEGIES TO CIRCUMVENT EFFLUX PUMPS

In response to the clinical shortcomings of small-molecule inhibitors, nanomedicine has introduced a suite of sophisticated strategies designed to fundamentally circumvent ABC transporter-mediated efflux. By encapsulating therapeutic agents within a nanoscale carrier, the drug's interaction with efflux pumps at the cell membrane can be minimized or altogether avoided. Nanoparticles primarily enter cells via endocytic pathways, a mechanism that bypasses the membrane-localized pumps. Once internalized, the nanocarrier releases its high-concentration payload directly into the cytoplasm, effectively overwhelming any remaining efflux capacity and ensuring the drug reaches its intracellular target. This section will explore the key multifunctional nanocarrier designs that leverage this principle, including the co-delivery of inhibitors, gene-silencing approaches, and stimuli-responsive systems.

A highly promising strategy involves the co-delivery of a chemotherapeutic agent and an ABC transporter inhibitor within a single nanocarrier system. This approach overcomes a major limitation of free-drug co-administration: the divergent pharmacokinetic and biodistribution profiles that prevent both agents from reaching the tumor in the optimal synergistic ratio. For instance, polymeric nanoparticles have been successfully engineered to co-encapsulate paclitaxel with sitravatinib, a potent inhibitor of both P-gp and BCRP, demonstrating marked synergy in resistant tumors [56], [57]. Similarly, liposomal formulations co-encapsulating doxorubicin and the third-generation inhibitor tariquidar have been shown to re-sensitize resistant cells more effectively than the administration of free drugs [58]. The primary strength of this approach lies in ensuring the spatiotemporal co-localization of the drug and inhibitor at the tumor site. However, a significant challenge remains in optimizing the drug-inhibitor ratio within the nanoparticle and controlling their respective release kinetics to ensure maximal therapeutic effect without causing off-target toxicity from the inhibitor.

An even more fundamental approach to disabling efflux pumps involves the use of nanocarriers to deliver gene-silencing therapeutics, such as small interfering RNA (siRNA), to suppress the expression of ABC transporter genes at the mRNA level. This strategy effectively tackles MDR at its source. Cationic platforms like dendrimers and lipid-based nanoparticles have been extensively studied for their ability to complex with and protect anionic siRNA molecules, delivering them to cancer cells to inhibit the translation of key transporter genes like *MDR1* (encoding P-gp). For example, studies utilizing siRNA-loaded dendrimers have demonstrated significant downregulation of *MDR1* mRNA and a corresponding increase in sensitivity to doxorubicin [59], [60]. Likewise, inorganic systems, such as gold nanoparticle-siRNA conjugates, have been designed for the targeted knockdown of *BCRP* [61]. While powerful in principle, the clinical translation of siRNA-based therapies faces hurdles, including the enzymatic degradation of siRNA,

the efficiency of endosomal escape, and the transient nature of the gene knockdown, which may require repeat administrations [62]. Future research must focus on designing more stable and efficient delivery vectors to realize the full potential of this approach.

Building on these concepts, advanced nanocarrier systems are being engineered to respond to specific triggers within the tumor microenvironment (TME), allowing for site-specific and on-demand drug release. The acidic nature of the TME (pH ~6.5-6.8) compared to healthy tissue (pH 7.4) is a widely exploited trigger. pH-sensitive nanogels and polymers can be designed to remain stable in systemic circulation but swell or disassemble upon protonation in the acidic TME, releasing their encapsulated drug or inhibitor payload precisely at the tumor site [63]. This not only enhances the therapeutic concentration where it is needed most but also minimizes systemic exposure and associated toxicities. The key advantage of stimuli-responsive systems is the gain in therapeutic specificity. The primary limitation, however, is the inherent heterogeneity of the TME; not all tumor regions are uniformly acidic, which could lead to inconsistent drug release [64].

To achieve an even higher degree of specificity, researchers are designing systems that respond to enzymes that are aberrantly overexpressed in the TME. Enzymes such as matrix metalloproteinases (MMPs), which are crucial for invasion and metastasis, serve as excellent targets. Nanoparticles can be engineered with drug-retaining linkers that are specifically cleaved by MMPs, ensuring that the therapeutic payload is released only in the enzyme-rich tumor vicinity. Other dysregulated metabolic enzymes associated with cancer progression, including certain lipogenic enzymes like fatty acid synthase (FASN) or key players in glycolysis like hexokinase 2 (HK2), also represent potential triggers. Enzymes like hexokinase 2 (HK2), lactate dehydrogenase (LDH), matrix metalloproteinases (MMPs), certain lipogenic enzymes like fatty acid synthase (FASN), glucose-6-phosphate isomerase (GPI), malic enzyme (ME), and isocitrate dehydrogenase (IDH), are also frequently overexpressed in tumors and contribute to cancer development [65]. While directly targeting intracellular enzymes with extracellular nanoparticles is complex, their activity often creates a unique metabolic signature (e.g., high concentrations of lactate or reactive oxygen species) that can be harnessed. The major strength of enzyme-responsive systems is their high biological specificity. However, this approach also faces challenges related to the heterogeneous expression of target enzymes across different tumor types and even within a single tumor mass.

Therefore, the development of multi-stimuli-responsive systems represents a critical future direction to create more robust and universally effective delivery platforms. By designing nanoparticles that require a dual trigger for activation, for instance, the acidic pH of the TME to prime the nanoparticle and a specific enzyme like MMP to execute drug release, thus a significantly higher level of tumor selectivity can be achieved. This "AND-gate" logic would minimize premature drug release in healthy tissues and concentrate the therapeutic effect at the intended site, representing a more intelligent and tailored approach to circumventing drug resistance.

## IV. EMERGING NANOTECHNOLOGIES AND INTELLIGENT SYSTEMS

Beyond established nanocarrier designs, the frontier of nanomedicine is rapidly advancing toward "intelligent" systems that exhibit unprecedented levels of autonomy, precision, and adaptability. These next-generation technologies are poised to transform the approach to combating MDR by integrating principles from robotics, cell biology, and artificial intelligence. They represent a paradigm shift from relatively static delivery vehicles to dynamic agents capable of sensing, processing, and responding to complex biological cues in real-time.

At the forefront of this evolution are nanoscale robots, or nanobots, which offer unparalleled precision in drug delivery. DNA origami, a technique that involves folding long strands of DNA into prescribed 2D and 3D shapes, has emerged as a leading platform for constructing these bots. Researchers have successfully designed DNA origami structures that act as logic-gated containers, remaining in a "locked" state until they recognize and bind to specific cancer biomarkers on the cell surface [66], [67]. This binding event triggers a conformational change, "unlocking" the nanobot to release its payload—such as a P-gp inhibitor or a potent chemotoxin—directly at the target cell. While this technology offers exquisite targeting capabilities, significant translational gaps persist, including the high cost of production, potential immunogenicity, and ensuring the structural integrity of these complex bots within the harsh *in vivo* environment.

Another innovative strategy employs a "Trojan horse" approach, hijacking the body's own cells to smuggle nanotherapeutics past formidable biological barriers. A compelling example is the use of neutrophils, which have a natural ability to cross the blood-brain barrier (BBB) to reach sites of inflammation. By loading drug-carrying nanoparticles into these immune cells, researchers have created "Trojanbots" capable of delivering therapies to notoriously difficult-to-treat brain tumors like glioblastoma [68]. Once the neutrophils have traversed the BBB, the nanoparticles can be released to target the tumor cells. This bio-inspired strategy is a powerful demonstration of how to overcome major physiological obstacles. Its primary limitations lie in the efficiency of nanoparticle loading into host cells without impairing their viability and function, and the potential to trigger unwanted inflammatory responses.

The sheer complexity of designing nanoparticles to navigate biological systems has necessitated the integration of artificial intelligence (AI) and machine learning (ML) into the development pipeline [69], [70]. AI-driven design can rapidly accelerate the optimization process, which is intractably slow using traditional trial-and-error methods [71]. By feeding large datasets from previous experiments into ML algorithms, it is possible to build predictive models that identify the optimal physicochemical properties, such as size, surface charge, and ligand density for a nanoparticle to achieve a specific goal, like enhanced tumor retention or maximal cellular uptake in resistant cells. This data-centric approach enables a more rational and efficient design of nanomedicines. The primary weakness of this field is its current reliance on large, high-quality, and standardized datasets, which are not always available. Future research

must not only focus on developing more sophisticated algorithms but also on generating the robust experimental data required to train them effectively.

## V. PRECLINICAL AND CLINICAL PROGRESS

The translation of multifunctional nanoparticles from conceptual designs to clinical realities is a complex, multi-stage process, yet the field has made substantial preclinical progress and seen foundational successes in clinical applications. The first generation of anticancer nanomedicines, such as Doxil® (liposomal doxorubicin) and Abraxane® (albumin-bound paclitaxel), demonstrated the core principle that nanoparticle encapsulation can improve the therapeutic index of chemotherapies [72], [73]. While not specifically designed to overcome MDR, their clinical approval established a crucial precedent and paved the way for more sophisticated systems. Current research, as summarized in Table 2, is focused on a diverse array of next-generation platforms that are explicitly engineered to combat ABC transporter-mediated resistance.

TABLE II. SELECTED PRECLINICAL STUDIES OF NANOPARTICLE PLATFORMS TARGETING ABC TRANSPORTER-MEDIATED DRUG RESISTANCE.

| Nanoplatform | Cancer Model | Key Outcome | Stage | Reference |
|---|---|---|---|---|
| Lipid-saporin nanoparticles (EC16-1/saporin) | ABCB1-overexpressing SW620/AD300 and ABCG2-overexpressing NCI-H460/MX20 xenografts | Significant tumor growth inhibition in both ABCB1 and ABCG2 resistant models; IC50 reduced to 2.50 ± 0.43 nM vs >50 nM for controls | Preclinical | [74] |
| Hyaluronan-grafted nanoparticle clusters (DOX-GAGs) | P-gp-overexpressing human ovarian adenocarcinoma xenograft model | Superior therapeutic effect over free doxorubicin in resistant tumor model; bypassed P-gp-mediated resistance mechanism | Preclinical | [75] |
| Polymeric AIEgen/P-gp siRNA nanoparticles (Py-TPE/siRNA@PMP) | SKOV-3/PTX resistant ovarian cancer and patient-derived xenografts (PDX) | Significant tumor growth suppression in subcutaneous, intraperitoneal metastasis, and PDX models; prolonged mouse survival vs controls | Preclinical | [76] |
| Hyaluronan-coated superparamagnetic iron oxide NPs (HA-SPIONs) | Drug-resistant human ovarian cancer cells (SKOV-3) | DOX accumulated at higher levels and distributed wider in tumor tissue than free DOX; significant reduction of tumor growth and extended survival | Preclinical | [77] |
| PLGA nanoparticles with SC-514 and 3-BPA | Prostate cancer cells with ABC transporter overexpression | Inhibited ATP Binding Cassette protein-mediated drug resistance; 50% reduction in chemotherapy failure | Preclinical | [78] |
| Lipid nanoparticle NBF-006 (GSTP siRNA) | Advanced NSCLC, pancreatic, and colorectal cancer patients | Disease control rate of 59% (19/38) in heavily pre-treated NSCLC patients; durable partial response in 2 patients | Phase I (NCT03819387) | [79], [80] |
| Polymeric micelles with paclitaxel (PT-R-Ms) | Solid tumors with P-glycoprotein efflux | 7.89-fold enhancement in PTX permeation; 8-fold increase in bioavailability; 42.9% apoptotic cells vs controls | Preclinical | [81] |
| Gold NP-siRNA conjugates (HsiRNA@PGD) | SKBR3 xenograft breast tumor model | Concurrent delivery of doxorubicin and HER2 siRNA; selective tumor accumulation with significant HER2 gene suppression | Preclinical | [82] |
| Dual-targeted nanoparticles (SSBPEI-DOX@siRNAs) | Ovarian cancer stem cells | Co-delivery of doxorubicin and siRNA cocktails (survivin, Bcl-2, ABCG2 siRNA); synergistic anti-CSC effects with drug resistance reversal | Preclinical | [83] |
| pH/ROS cascade-responsive nanoparticles (PLP-NPs) | Multidrug-resistant colon cancer | Downregulated P-glycoprotein production through NQO1 activity; overcame MDR with tumor-specific cytotoxicity in vivo | Preclinical | [84] |
| Trimethyl-chitosan coated gold NPs (AuNPs-TMC) | MCF-7 breast cancer cells | 86% gene expression knockdown of EGFR; 50% cell viability reduction; complete cellular uptake after 4h | Preclinical | [85] |
| Albumin nanoparticles with piperine-paclitaxel (PP@AN) | Multidrug-resistant triple-negative breast cancer | Enhanced PTX sensitivity through P-gp inhibition; significant increase in drug accumulation and P-gp downregulation at 1:2 ratio | Preclinical | [86] |
| Polymeric nanoparticle micellar paclitaxel (PM-Pac) | Stage III-IV high-grade serous ovarian cancer patients | Improved progression-free survival: median 35.5 vs 28.1 months compared to conventional paclitaxel | Clinical retrospective study | [87] |
| Curcumin-paclitaxel core-shell nanoparticles | Drug-resistant ovarian cancer (SKOV3-TR30) | Synergistic anti-ovarian cancer effects; reversed drug resistance by inhibiting P-gp efflux and tumor cell migration | Preclinical | [88] |
| RNA nanoparticles with HER2 aptamers (XBP1 siRNA) | HER2+ breast cancer mouse model | Strongly bound to tumors; XBP1 deletion impaired angiogenesis and promoted chemotherapy sensitization | Preclinical | [89] |

A comprehensive review of preclinical studies reveals a field rich with innovation, successfully demonstrating proof-of-concept across a wide range of models (Table 2). Liposomal and polymeric nanoparticles remain the most mature and widely studied platforms due to their biocompatibility and versatile chemistry. For example, the co-delivery of doxorubicin and curcumin (a natural P-gp inhibitor) in liposomes has been shown to significantly increase apoptosis in resistant MCF-7/ADR breast cancer cells compared to free doxorubicin [90]. Similarly, polymeric micelles co-loading paclitaxel and the P-gp inhibitor pluronic have demonstrated superior tumor growth inhibition in xenograft models of drug-resistant ovarian cancer [91]. These studies provide strong evidence that the co-encapsulation strategy effectively re-sensitizes resistant tumors to conventional chemotherapy. The strength of this body of work lies in the consistent validation of these concepts *in vitro* and in animal models; its primary weakness is that very

few of these highly specific, multifunctional systems have advanced to clinical trials.

Despite the wealth of promising preclinical data, the journey to clinical approval is fraught with challenges, including manufacturing scalability, batch-to-batch consistency, long-term toxicity concerns, and the immense cost of clinical trials. The most significant gap between preclinical success and clinical application is the "bench-to-bedside" transition. While many systems, such as the mesoporous silica nanoparticles designed for stimuli-responsive cisplatin release (Table 2), show remarkable efficacy in controlled laboratory settings, their behavior in the heterogeneous human patient population is difficult to predict [92]. Therefore, a critical future direction is the development of more predictive preclinical models, such as patient-derived xenografts (PDXs) and complex organ-on-a-chip systems, that better replicate human tumor biology and the systemic effects of nanomedicines. Furthermore, a concerted effort is needed to standardize regulatory pathways for these complex combination products, which will be essential to streamline their clinical development and ultimately realize their therapeutic potential for patients with drug-resistant cancer.

## VI. CHALLENGES AND FUTURE DIRECTIONS

Despite the immense promise and rapid pace of innovation, the widespread clinical translation of multifunctional nanoparticles for MDR reversal faces significant biological, technical, and regulatory hurdles. These challenges must be systematically addressed to bridge the gap between compelling preclinical data and routine clinical use. The future of the field will depend on developing a deeper understanding of nanoparticle-host interactions, creating robust and scalable manufacturing processes, and designing smarter, more predictive therapeutic platforms.

A primary biological barrier is the complex and often unpredictable interaction of nanoparticles with the host physiological system, leading to concerns regarding toxicity and immunogenicity. Upon entering the bloodstream, nanoparticles are immediately coated with a layer of host proteins, forming a "protein corona" that alters their original engineered identity [93]. This bio-corona can fundamentally change the nanoparticle's biodistribution, clearance rate, and cellular uptake, often directing them away from the tumor and toward organs of the reticuloendothelial system like the liver and spleen, thus limiting efficacy and potentially causing off-target toxicity. Mitigating these effects, perhaps through the design of advanced "stealth" coatings or by pre-saturating the corona with specific proteins, remains a critical area of investigation [94].

From a technical standpoint, manufacturing and regulatory approval present formidable challenges. The complexity of multifunctional nanoparticles, often involving multiple components like polymers, lipids, drugs, and genetic material; makes large-scale, reproducible manufacturing under Good Manufacturing Practice (GMP) standards incredibly difficult. There is a pressing lack of standardized protocols and quality control metrics for characterizing these hybrid systems, which complicates regulatory evaluation. National and international regulatory bodies are still adapting to these novel therapeutic modalities, and establishing clear, predictable pathways for clinical approval is essential for encouraging investment and innovation in the field [95].

Looking forward, the next generation of nanotherapeutics will likely be defined by enhanced biomimicry and greater integration of diagnostic and therapeutic functions. A key priority is the development and adoption of more sophisticated preclinical models that can better predict clinical outcomes. Organ-on-chip platforms that incorporate 3D cell cultures, physiological fluid flow, and multiple cell types are emerging as powerful tools for studying nanoparticle transport and efficacy in a human-relevant context, especially for MDR studies [96], [97], [98]. Furthermore, the convergence of diagnostics and therapy into single "theranostic" platforms represents a major advance. Future research will focus on creating modular nanoparticles that can not only deliver a therapeutic payload to inhibit efflux pumps but also carry agents to confirm delivery, monitor tumor response, and stratify patients who are most likely to benefit, thus paving the way for a new era of personalized nanomedicine against drug-resistant cancer.

## VII. CONCLUSION

ABC transporter-mediated multidrug resistance remains a linchpin in chemotherapy failure, driving tumor recurrence through efflux pump overexpression that compromises therapeutic efficacy. This sudy has synthesized compelling evidence that multifunctional nanoparticles represent a paradigm-shifting approach to circumvent this resistance through rational engineering and combinatorial mechanisms. Key advancements include nanocarriers that co-deliver chemotherapeutics with ABC inhibitors to ensure spatiotemporal co-localization, gene-silencing platforms that downregulate transporter expression, and stimuli-responsive systems that exploit tumor microenvironment cues for site-specific payload release. Emerging technologies such as DNA nanobots and neutrophil-guided "Trojanbots" further demonstrate unprecedented precision in overcoming biological barriers. Collectively, these innovations substantially enhance intracellular drug accumulation while minimizing systemic toxicity, effectively re-sensitizing resistant malignancies to conventional therapies.

Despite these promising developments, significant challenges impede clinical translation. The formation of protein coronas unpredictably alters nanoparticle biodistribution, diverting substantial doses to reticuloendothelial organs and compromising tumor targeting. Manufacturing complexities inherent to hybrid nanosystems particularly those integrating polymeric, inorganic, and biological components, hinder scalable Good Manufacturing Practice (GMP) production and batch consistency. Moreover, the stark discrepancy between preclinical success and clinical performance underscores the limitations of current animal models in replicating human tumor heterogeneity and transporter redundancy. Fewer multifunctional nanotherapeutics advance beyond Phase I trials, reflecting inadequate predictive validity of existing evaluation frameworks.

Future research must prioritize four critical avenues:

1. **Advanced Biomimicry**: Developing "stealth" nanoparticles with pre-saturated protein coronas to evade immune recognition and enhance tumor-specific accumulation.

2. **Multi-Stimuli Systems**: Engineering nanoplatforms responsive to dual tumor microenvironment triggers (e.g., pH/enzyme or redox/hypoxia) to ensure uniform drug release in heterogeneous lesions.
3. **Integrated Theranostics**: Combining efflux inhibitors with real-time monitoring agents (e.g., MRI/PET tracers) to monitor biodistribution and therapeutic response simultaneously.
4. **Personalized Approaches**: Creating modular nanoparticles adaptable to patient-specific transporter profiles using AI-driven design and validated through physiologically relevant models like patient-derived xenografts (PDXs) and multi-organ chips.

The transformative potential of multifunctional nanoparticles necessitates interdisciplinary collaboration to standardize regulatory pathways, optimize scalable synthesis, and validate clinical efficacy in malignancies with proven efflux redundancy (e.g., ovarian and triple-negative breast cancers). Concerted efforts in these domains will accelerate the transition from proof-of-concept to clinically viable solutions, ultimately ushering in an era of precision nanomedicine for drug-resistant oncology.

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## REFERENCES

[1] R. L. Siegel, K. D. Miller, H. E. Fuchs, and A. Jemal, 'Cancer statistics, 2022', *CA Cancer J Clin*, vol. 72, no. 1, pp. 7–33, Jan. 2022, doi: 10.3322/caac.21708.

[2] C. Duan, M. Yu, J. Xu, B.-Y. Li, Y. Zhao, and R. K. Kankala, 'Overcoming Cancer Multi-drug Resistance (MDR): Reasons, mechanisms, nanotherapeutic solutions, and challenges', *Biomedicine & Pharmacotherapy*, vol. 162, p. 114643, Jun. 2023, doi: 10.1016/j.biopha.2023.114643.

[3] W. Zhang, Z. Zhu, and Y. Liu, 'The impact of the ATP-binding cassette (ABC) transporter family on multidrug resistance in head and neck tumors', *Mol Biol Rep*, vol. 52, no. 1, p. 256, Dec. 2025, doi: 10.1007/s11033-025-10321-9.

[4] J. Wang *et al.*, 'ATP-binding cassette (ABC) transporters in cancer: A review of recent updates', *J Evid Based Med*, vol. 14, no. 3, pp. 232–256, Sep. 2021, doi: 10.1111/jebm.12434.

[5] F. J. Sharom, 'ABC Multidrug Transporters: Structure, Function and Role in Chemoresistance', *Pharmacogenomics*, vol. 9, no. 1, pp. 105–127, Jan. 2008, doi: 10.2217/14622416.9.1.105.

[6] L. E. Russell *et al.*, 'Transporter-mediated drug-drug interactions: regulatory guidelines, *in vitro* and *in vivo* methodologies and translation, special populations, and the blood-brain barrier', *Drug Metab Rev*, pp. 1–28, Jul. 2024, doi: 10.1080/03602532.2024.2364591.

[7] S. Ashique, A. Garg, A. Hussain, A. Farid, P. Kumar, and F. Taghizadeh-Hesary, 'Nanodelivery systems: An efficient and target-specific approach for drug-resistant cancers', *Cancer Med*, vol. 12, no. 18, pp. 18797–18825, Sep. 2023, doi: 10.1002/cam4.6502.

[8] M. Dean, K. Moitra, and R. Allikmets, 'The human ATP-binding cassette (ABC) transporter superfamily', *Hum Mutat*, vol. 43, no. 9, pp. 1162–1182, Sep. 2022, doi: 10.1002/humu.24418.

[9] M. Feyzizadeh, A. Barfar, Z. Nouri, M. Sarfraz, P. Zakeri-Milani, and H. Valizadeh, 'Overcoming multidrug resistance through targeting ABC transporters: lessons for drug discovery', *Expert Opin Drug Discov*, vol. 17, no. 9, pp. 1013–1027, Sep. 2022, doi: 10.1080/17460441.2022.2112666.

[10] M. Chen *et al.*, 'ABC Transporters and CYP3A4 Mediate Drug Interactions between Enrofloxacin and Salinomycin Leading to Increased Risk of Drug Residues and Resistance', *Antibiotics*, vol. 12, no. 2, p. 403, Feb. 2023, doi: 10.3390/antibiotics12020403.

[11] K. Kiełbowski, M. Król, E. Bakinowska, and A. Pawlik, 'The Role of ABCB1, ABCG2, and SLC Transporters in Pharmacokinetic Parameters of Selected Drugs and Their Involvement in Drug–Drug Interactions', *Membranes (Basel)*, vol. 14, no. 11, p. 223, Oct. 2024, doi: 10.3390/membranes14110223.

[12] J. Marin *et al.*, 'Expression of Chemoresistance-Associated ABC Proteins in Hepatobiliary, Pancreatic and Gastrointestinal Cancers', *Cancers (Basel)*, vol. 14, no. 14, p. 3524, Jul. 2022, doi: 10.3390/cancers14143524.

[13] A. Modi *et al.*, 'ABC transporters in breast cancer: their roles in multidrug resistance and beyond', *J Drug Target*, vol. 30, no. 9, pp. 927–947, Oct. 2022, doi: 10.1080/1061186X.2022.2091578.

[14] J.-Q. Wang *et al.*, 'Establishment and Characterization of a Novel Multidrug Resistant Human Ovarian Cancer Cell Line With Heterogenous MRP7 Overexpression', *Front Oncol*, vol. 11, p. 731260, Sep. 2021, doi: 10.3389/fonc.2021.731260.

[15] Y.-L. Chen, T.-Y. Yang, K.-C. Chen, C.-L. Wu, S.-L. Hsu, and C.-M. Hsueh, 'Hypoxia can impair doxorubicin resistance of non-small cell lung cancer cells by inhibiting MRP1 and P-gp expression and boosting the chemosensitizing effects of MRP1 and P-gp blockers', *Cellular Oncology*, vol. 39, no. 5, pp. 411–433, Oct. 2016, doi: 10.1007/s13402-016-0285-5.

[16] A. Jain and S. K. Jain, *Nanomedicine and Tissue Engineering*. Apple Academic Press, 2016. doi: 10.1201/b19867.

[17] H. M. Abdallah, A. M. Al-Abd, R. S. El-Dine, and A. M. El-Halawany, 'P-glycoprotein inhibitors of natural origin as potential tumor chemo-sensitizers: A review', *J Adv Res*, vol. 6, no. 1, pp. 45–62, Jan. 2015, doi: 10.1016/j.jare.2014.11.008.

[18] G.-E. Fathy Abd-Ellatef *et al.*, 'Curcumin-Loaded Solid Lipid Nanoparticles Bypass P-Glycoprotein Mediated Doxorubicin Resistance in Triple Negative Breast Cancer Cells', *Pharmaceutics*, vol. 12, no. 2, p. 96, Jan. 2020, doi: 10.3390/pharmaceutics12020096.

[19] I.-T. Wu, C.-Y. Kuo, C.-H. Su, Y.-H. Lan, and C.-C. Hung, 'Pinostrobin and Tectochrysin Conquer Multidrug-Resistant Cancer Cells via Inhibiting P-Glycoprotein ATPase', *Pharmaceuticals*, vol. 16, no. 2, p. 205, Jan. 2023, doi: 10.3390/ph16020205.

[20] R. Tang *et al.*, 'Zosuquidar restores drug sensitivity in P-glycoprotein expressing acute myeloid leukemia (AML)', *BMC Cancer*, vol. 8, no. 1, p. 51, Dec. 2008, doi: 10.1186/1471-2407-8-51.

[21] A. Sajid *et al.*, 'Reversing the direction of drug transport mediated by the human multidrug transporter P-glycoprotein', *Proceedings of the National Academy of Sciences*, vol. 117, no. 47, pp. 29609–29617, Nov. 2020, doi: 10.1073/pnas.2016270117.

[22] W. Sun *et al.*, 'In Vivo Reversal of P-Glycoprotein-Mediated Drug Resistance in a Breast Cancer Xenograft and in Leukemia Models Using a Novel, Potent, and Nontoxic Epicatechin EC31', *Int J Mol Sci*, vol. 24, no. 5, p. 4377, Feb. 2023, doi: 10.3390/ijms24054377.

[23] D. Linke *et al.*, 'Comprehensive Evaluation of Multiple Approaches Targeting ABCB1 to Resensitize Docetaxel-Resistant Prostate Cancer Cell Lines', *Int J Mol Sci*, vol. 24, no. 1, p. 666, Dec. 2022, doi: 10.3390/ijms24010666.

[24] R. Bakadlag, G. Limniatis, G. Georges, and E. Georges, 'The anti-estrogen receptor drug, tamoxifen, is selectively Lethal to P-glycoprotein-expressing Multidrug resistant tumor cells', *BMC Cancer*, vol. 23, no. 1, p. 24, Jan. 2023, doi: 10.1186/s12885-022-10474-x.

[25] R. Maia, F. Vasconcelos, P. Souza, and V. Rumjanek, 'Towards Comprehension of the ABCB1/P-Glycoprotein Role in Chronic Myeloid Leukemia', *Molecules*, vol. 23, no. 1, p. 119, Jan. 2018, doi: 10.3390/molecules23010119.

[26] G. Caceres *et al.*, 'In Vitro and In Vivo Inhibition of P-Glycoprotein (ABCB1) by a Novel Non-Substrate Compound: HG-829', *Blood*,

vol. 116, no. 21, pp. 3986–3986, Nov. 2010, doi: 10.1182/blood.V116.21.3986.3986.
[27] G. Caceres *et al.*, 'HG-829 Is a Potent Noncompetitive Inhibitor of the ATP-Binding Cassette Multidrug Resistance Transporter *ABCB1*', *Cancer Res*, vol. 72, no. 16, pp. 4204–4213, Aug. 2012, doi: 10.1158/0008-5472.CAN-12-0743.
[28] Y.-N. Teng, Y.-H. Wang, T.-S. Wu, H.-Y. Hung, and C.-C. Hung, 'Zhankuic Acids A, B and C from Taiwanofungus camphoratus Act as Cytotoxicity Enhancers by Regulating P-Glycoprotein in Multi-Drug Resistant Cancer Cells', *Biomolecules*, vol. 9, no. 12, p. 759, Nov. 2019, doi: 10.3390/biom9120759.
[29] M. Deng, K. Qin, Y. Li, Y. Jiang, W. Jin, and Z. Shen, 'Abstract 5338: Pamiparib as a non-P-glycoprotein substrate PARP inhibitor can overcome *ABCB1* -mediated multidrug resistance in ovarian cancer cells', *Cancer Res*, vol. 82, no. 12_Supplement, pp. 5338–5338, Jun. 2022, doi: 10.1158/1538-7445.AM2022-5338.
[30] H. Rahman, M. J. Ware, A. Sajid, S. Lusvarghi, S. R. Durell, and S. V. Ambudkar, 'Residues from Homologous Transmembrane Helices 4 and 10 Are Critical for P-Glycoprotein (ABCB1)-Mediated Drug Transport', *Cancers (Basel)*, vol. 15, no. 13, p. 3459, Jul. 2023, doi: 10.3390/cancers15133459.
[31] Y. Qian *et al.*, 'Abstract 2621: Growth hormone receptor antagonist sensitizes melanoma and hepatocarcinoma to drug treatments via downregulation of ABC transporters in vivo', *Cancer Res*, vol. 82, no. 12_Supplement, pp. 2621–2621, Jun. 2022, doi: 10.1158/1538-7445.AM2022-2621.
[32] R. Basu *et al.*, 'Growth hormone receptor antagonism downregulates ATP-binding cassette transporters contributing to improved drug efficacy against melanoma and hepatocarcinoma in vivo', *Front Oncol*, vol. 12, p. 936145, Jul. 2022, doi: 10.3389/fonc.2022.936145.
[33] A. Tamaki, C. Ierano, G. Szakacs, R. W. Robey, and S. E. Bates, 'The controversial role of ABC transporters in clinical oncology', *Essays Biochem*, vol. 50, no. 1, pp. 209–232, Sep. 2011, doi: 10.1042/bse0500209.
[34] Gattass, 'Betulinic acid does not modulate the activity of P-gp/ABCB1 or MRP1/ABCC1 in a non-tumoral renal cell line: Possible utility in multidrug resistance cancer chemotherapy', *Mol Med Rep*, vol. 2, no. 2, pp. 271–275, Feb. 2009, doi: 10.3892/mmr_00000095.
[35] F. C. A. DE Moraes, M. E. C. Souza, E. R. DA Silva, M. Kreuz, and R. M. R. Burbano, 'Impact of ABCG2 rs2231142(421C>A) Variant on the Clinical Outcomes of Patients With EGFR-mutated Non-small Cell Lung Cancer Treated With Gefitinib: A Comprehensive Meta-analysis.', *Anticancer Res*, vol. 44, no. 12, pp. 5361–5370, Dec. 2024, doi: 10.21873/anticanres.17363.
[36] J. Peng, M. K. Ladumor, and J. D. Unadkat, 'Estimation of Fetal-to-Maternal Unbound Steady-State Plasma Concentration Ratio of P-Glycoprotein and/or Breast Cancer Resistance Protein Substrate Drugs Using a Maternal-Fetal Physiologically Based Pharmacokinetic Model', *Drug Metabolism and Disposition*, vol. 50, no. 5, pp. 613–623, May 2022, doi: 10.1124/dmd.121.000733.
[37] S. Chatterjee, A. A. Deshpande, and H. Shen, 'Recent advances in the *in vitro* and *in vivo* methods to assess impact of P-glycoprotein and breast cancer resistance protein transporters in central nervous system drug disposition', *Biopharm Drug Dispos*, vol. 44, no. 1, pp. 7–25, Feb. 2023, doi: 10.1002/bdd.2345.
[38] J. Goebel, J. Chmielewski, and C. A. Hrycyna, 'The roles of the human ATP-binding cassette transporters P-glycoprotein and ABCG2 in multidrug resistance in cancer and at endogenous sites: future opportunities for structure-based drug design of inhibitors', *Cancer Drug Resistance*, vol. 4, no. 4, pp. 784–804, Aug. 2021, doi: 10.20517/cdr.2021.19.
[39] B. Poller, E. Wagenaar, S. C. Tang, and A. H. Schinkel, 'Double-Transduced MDCKII Cells To Study Human P-Glycoprotein (ABCB1) and Breast Cancer Resistance Protein (ABCG2) Interplay in Drug Transport across the Blood−Brain Barrier', *Mol Pharm*, vol. 8, no. 2, pp. 571–582, Apr. 2011, doi: 10.1021/mp1003898.
[40] A. Poustforoosh and F. Moosavi, 'Evaluation of the FDA-approved kinase inhibitors to uncover the potential repurposing candidates targeting ABC transporters in multidrug-resistant cancer cells: an in silico approach', *J Biomol Struct Dyn*, vol. 42, no. 24, pp. 13650–13662, Dec. 2024, doi: 10.1080/07391102.2023.2277848.
[41] D. Westover and F. Li, 'New trends for overcoming ABCG2/BCRP-mediated resistance to cancer therapies.', *J Exp Clin Cancer Res*, vol. 34, no. 1, p. 159, Dec. 2015, doi: 10.1186/s13046-015-0275-x.
[42] M. Wada, 'Role of ABC Transporters in Cancer Development and Malignant Alteration', *YAKUGAKU ZASSHI*, vol. 142, no. 11, pp. 22–00108, Nov. 2022, doi: 10.1248/yakushi.22-00108.
[43] K. Gronkowska, S. Michlewska, and A. Robaszkiewicz, 'Activity of Lysosomal ABCC3, ABCC5 and ABCC10 is Responsible for Lysosomal Sequestration of Doxorubicin and Paclitaxel-Oregongreen488 in Paclitaxel-Resistant Cancer Cell Lines', *Cellular Physiology and Biochemistry*, vol. 57, no. 5, pp. 360–378, Sep. 2023, doi: 10.33594/000000663.
[44] A. Modi *et al.*, 'ABC transporters in breast cancer: their roles in multidrug resistance and beyond', *J Drug Target*, vol. 30, no. 9, pp. 927–947, Oct. 2022, doi: 10.1080/1061186X.2022.2091578.
[45] A. Alam and K. P. Locher, 'Structure and Mechanism of Human ABC Transporters', *Annu Rev Biophys*, vol. 52, no. 1, pp. 275–300, May 2023, doi: 10.1146/annurev-biophys-111622-091232.
[46] W. Fan, K. Shao, and M. Luo, 'Structural View of Cryo-Electron Microscopy-Determined ATP-Binding Cassette Transporters in Human Multidrug Resistance', *Biomolecules*, vol. 14, no. 2, p. 231, Feb. 2024, doi: 10.3390/biom14020231.
[47] D. Januliene and A. Moeller, 'Cryo-EM of ABC transporters: an ice-cold solution to everything?', *FEBS Lett*, vol. 594, no. 23, pp. 3776–3789, Dec. 2020, doi: 10.1002/1873-3468.13989.
[48] D. Kurre, P. X. Dang, L. T. M. Le, V. V Gadkari, and A. Alam, 'Structural insights into binding-site access and ligand recognition by human ABCB1', *EMBO J*, vol. 44, no. 4, pp. 991–1006, Jan. 2025, doi: 10.1038/S44318-025-00361-Z.
[49] M. Li, I. A. M. de Graaf, M. H. de Jager, and G. M. M. Groothuis, 'P-gp activity and inhibition in the different regions of human intestine ex vivo', *Biopharm Drug Dispos*, vol. 38, no. 2, pp. 127–138, Mar. 2017, doi: 10.1002/BDD.2047.
[50] L. Wang and Y. Sun, 'Efflux mechanism and pathway of verapamil pumping by human P-glycoprotein', *Arch Biochem Biophys*, vol. 696, p. 108675, Dec. 2020, doi: 10.1016/J.ABB.2020.108675.
[51] L. Saaby, P. Tfelt-Hansen, and B. Brodin, 'The putative P-gp inhibitor telmisartan does not affect the transcellular permeability and cellular uptake of the calcium channel antagonist verapamil in the P-glycoprotein expressing cell line MDCK II MDR1', *Pharmacol Res Perspect*, vol. 3, no. 4, p. e00151, Aug. 2015, doi: 10.1002/PRP2.151;JOURNAL:JOURNAL:20521707;CTYPE:STRING:JOURNAL.
[52] G. Pinto *et al.*, 'Comparative Influences of Beta blockers and Verapamil on Cardiac Outcomes in Hypertrophic Cardiomyopathy', *Am J Cardiol*, vol. 235, pp. 9–15, Jan. 2025, doi: 10.1016/J.AMJCARD.2024.10.029.
[53] Y. Gao *et al.*, 'Membrane-assisted tariquidar access and binding mechanisms of human ATP-binding cassette transporter P-glycoprotein', *Front Mol Biosci*, vol. 11, p. 1364494, Mar. 2024, doi: 10.3389/FMOLB.2024.1364494/BIBTEX.
[54] C. Rowbottom *et al.*, 'Optimization of dose and route of administration of the P-glycoprotein inhibitor, valspodar (PSC-833) and the P-glycoprotein and breast cancer resistance protein dual-inhibitor, elacridar (GF120918) as dual infusion in rats', *Pharmacol Res Perspect*, vol. 9, no. 2, p. e00740, Apr. 2021, doi: 10.1002/PRP2.740.
[55] P. Sharma, N. Singh, and S. Sharma, 'ATP Binding Cassette Transporters and Cancer: Revisiting Their Controversial Role', *Pharmacogenomics*, vol. 22, no. 18, pp. 1211–1235, Dec. 2021, doi: 10.2217/pgs-2021-0116.
[56] C. Sorrentino, S. L. Ciummo, C. Fieni, and E. Di Carlo, 'Nanomedicine for cancer patient-centered care', *MedComm (Beijing)*, vol. 5, no. 11, p. e767, Nov. 2024, doi: 10.1002/mco2.767.
[57] P. Yadav, S. V. Ambudkar, and N. Rajendra Prasad, 'Emerging nanotechnology-based therapeutics to combat multidrug-resistant cancer', *J Nanobiotechnology*, vol. 20, no. 1, p. 423, Sep. 2022, doi: 10.1186/s12951-022-01626-z.
[58] P. S. Chary *et al.*, 'Nanotechnology', in *Multifunctional Nanocarriers*, Elsevier, 2022, pp. 1–24. doi: 10.1016/B978-0-323-85041-4.00022-6.
[59] M. D. A. Paskeh *et al.*, 'Overcoming doxorubicin resistance in cancer: siRNA-loaded nanoarchitectures for cancer gene therapy', *Life Sci*, vol. 298, p. 120463, Jun. 2022, doi: 10.1016/j.lfs.2022.120463.
[60] J. Pan *et al.*, 'Polyamidoamine dendrimers-based nanomedicine for combination therapy with siRNA and chemotherapeutics to overcome multidrug resistance', *European Journal of Pharmaceutics and*

*Biopharmaceutics*, vol. 136, pp. 18–28, Mar. 2019, doi: 10.1016/j.ejpb.2019.01.006.

[61] D. Jain, S. K. Prajapati, A. Jain, and R. Singhal, 'Nano-formulated siRNA-based therapeutic approaches for cancer therapy', *Nano Trends*, vol. 1, p. 100006, Mar. 2023, doi: 10.1016/j.nwnano.2023.100006.

[62] M. I. Sajid, M. Moazzam, S. Kato, K. Yeseom Cho, and R. K. Tiwari, 'Overcoming Barriers for siRNA Therapeutics: From Bench to Bedside', *Pharmaceuticals*, vol. 13, no. 10, p. 294, Oct. 2020, doi: 10.3390/ph13100294.

[63] D. Singh, B. Das Kurmi, A. Singh, and S. Bhattacharya, 'pH-Sensitive Macromolecular Carriers: Targeted Therapeutics for Cancer and Inflammation', *Journal of Macromolecular Science, Part B*, pp. 1–11, Feb. 2025, doi: 10.1080/00222348.2025.2466325.

[64] Y.-C. Fu, S.-B. Liang, M. Luo, and X.-P. Wang, 'Intratumoral heterogeneity and drug resistance in cancer', *Cancer Cell Int*, vol. 25, no. 1, p. 103, Mar. 2025, doi: 10.1186/s12935-025-03734-w.

[65] H. Kapalatiya, Y. Madav, V. S. Tambe, and S. Wairkar, 'Enzyme-responsive smart nanocarriers for targeted chemotherapy: an overview', *Drug Deliv Transl Res*, vol. 12, no. 6, pp. 1293–1305, Jun. 2022, doi: 10.1007/s13346-021-01020-6.

[66] I. Domljanovic, M. Loretan, S. Kempter, G. P. Acuna, S. Kocabey, and C. Ruegg, 'DNA origami book biosensor for multiplex detection of cancer-associated nucleic acids', *Nanoscale*, vol. 14, no. 41, pp. 15432–15441, Oct. 2022, doi: 10.1039/D2NR03985K.

[67] C. Yuan *et al.*, 'Functionalized DNA Origami-Enabled Detection of Biomarkers', *ChemBioChem*, vol. 25, no. 13, p. e202400227, Jul. 2024, doi: 10.1002/cbic.202400227.

[68] M. Ijaz *et al.*, 'Combinatory Immunotherapy for Glioblastoma Treatment', *Adv Ther (Weinh)*, vol. 7, no. 11, p. 2400217, Nov. 2024, doi: 10.1002/adtp.202400217.

[69] S. Gupta, U. Gupta, M. Sharma, and K. Malik, *Generative Intelligence in Healthcare*. Boca Raton: CRC Press, 2025. doi: 10.1201/9781003539483.

[70] M. Shirzad *et al.*, 'Artificial Intelligence-Assisted Design of Nanomedicines for Breast Cancer Diagnosis and Therapy: Advances, Challenges, and Future Directions', *Bionanoscience*, vol. 15, no. 3, p. 354, Sep. 2025, doi: 10.1007/s12668-025-01980-w.

[71] Q. Wang, Y. Liu, C. Li, B. Xu, S. Xu, and B. Liu, 'Machine Learning-Enhanced Nanoparticle Design for Precision Cancer Drug Delivery', *Advanced Science*, p. e03138, Jun. 2025, doi: 10.1002/advs.202503138.

[72] J. Venturini, A. Chakraborty, M. A. Baysal, and A. M. Tsimberidou, 'Developments in nanotechnology approaches for the treatment of solid tumors', *Exp Hematol Oncol*, vol. 14, no. 1, p. 76, May 2025, doi: 10.1186/s40164-025-00656-1.

[73] R. Ganpisetti *et al.*, 'Biological Nanocarriers in Cancer Therapy: Cutting Edge Innovations in Precision Drug Delivery', *Biomolecules*, vol. 15, no. 6, p. 802, May 2025, doi: 10.3390/biom15060802.

[74] G.-N. Zhang *et al.*, 'Lipid–Saporin Nanoparticles for the Intracellular Delivery of Cytotoxic Protein to Overcome ABC Transporter-Mediated Multidrug Resistance In Vitro and In Vivo', *Cancers (Basel)*, vol. 12, no. 2, p. 498, Feb. 2020, doi: 10.3390/cancers12020498.

[75] K. Cohen, R. Emmanuel, E. Kisin-Finfer, D. Shabat, and D. Peer, 'Modulation of Drug Resistance in Ovarian Adenocarcinoma Using Chemotherapy Entrapped in Hyaluronan-Grafted Nanoparticle Clusters', *ACS Nano*, vol. 8, no. 3, pp. 2183–2195, Mar. 2014, doi: 10.1021/nn500205b.

[76] J. Wu *et al.*, 'Biocompatible AIEgen/p-glycoprotein siRNA@reduction-sensitive paclitaxel polymeric prodrug nanoparticles for overcoming chemotherapy resistance in ovarian cancer', *Theranostics*, vol. 11, no. 8, pp. 3710–3724, 2021, doi: 10.7150/thno.53828.

[77] M. H. El-Dakdouki *et al.*, 'Assessing the *in Vivo* Efficacy of Doxorubicin Loaded Hyaluronan Nanoparticles', *ACS Appl Mater Interfaces*, vol. 6, no. 1, pp. 697–705, Jan. 2014, doi: 10.1021/am404946v.

[78] T. O. Famuyiwa, 'ABC Transporter-Mediated Multidrug Resistance in Prostate Cancer Cells', *The FASEB Journal*, vol. 33, no. S1, pp. 647.6-647.6, Apr. 2019, doi: 10.1096/fasebj.2019.33.1_supplement.647.6.

[79] L. Bazhenova *et al.*, 'Abstract CT040: First-in-human dose-expansion study of NBF-006, a novel investigational siRNA targeting GSTP, in patients with KRAS-mutated non-small cell lung cancer', *Cancer Res*, vol. 84, no. 7_Supplement, pp. CT040–CT040, Apr. 2024, doi: 10.1158/1538-7445.AM2024-CT040.

[80] A. W. Tolcher *et al.*, 'First-in-human dose-escalation study of NBF-006, a novel investigational siRNA targeting GSTP, in patients with non-small cell lung, pancreatic, or colorectal cancer.', *Journal of Clinical Oncology*, vol. 41, no. 16_suppl, pp. 3084–3084, Jun. 2023, doi: 10.1200/JCO.2023.41.16_suppl.3084.

[81] S. Razzaq *et al.*, 'A Multifunctional Polymeric Micelle for Targeted Delivery of Paclitaxel by the Inhibition of the P-Glycoprotein Transporters', *Nanomaterials*, vol. 11, no. 11, p. 2858, Oct. 2021, doi: 10.3390/nano11112858.

[82] A. M. G. *et al.*, 'HER2 siRNA Facilitated Gene Silencing Coupled with Doxorubicin Delivery: A Dual Responsive Nanoplatform Abrogates Breast Cancer', *ACS Appl Mater Interfaces*, vol. 16, no. 20, pp. 25710–25726, May 2024, doi: 10.1021/acsami.4c02532.

[83] L. Chen *et al.*, 'Dual Targeted Nanoparticles for the Codelivery of Doxorubicin and siRNA Cocktails to Overcome Ovarian Cancer Stem Cells', *Int J Mol Sci*, vol. 24, no. 14, p. 11575, Jul. 2023, doi: 10.3390/IJMS241411575/S1.

[84] N. Chang, Y. Zhao, N. Ge, and L. Qian, 'A pH/ROS cascade-responsive and self-accelerating drug release nanosystem for the targeted treatment of multi-drug-resistant colon cancer', *Drug Deliv*, vol. 27, no. 1, pp. 1073–1086, Jan. 2020, doi: 10.1080/10717544.2020.1797238.

[85] L. Baghani, N. Noroozi Heris, F. Khonsari, S. Dinarvand, M. Dinarvand, and F. Atyabi, 'Trimethyl-Chitosan Coated Gold Nanoparticles Enhance Delivery, Cellular Uptake and Gene Silencing Effect of EGFR-siRNA in Breast Cancer Cells', *Front Mol Biosci*, vol. 9, p. 871541, Apr. 2022, doi: 10.3389/FMOLB.2022.871541/BIBTEX.

[86] W. Xu, Y. Xiao, L. Zheng, M. Xu, X. Jiang, and L. Wang, 'Enhancing Paclitaxel Efficacy with Piperine-Paclitaxel Albumin Nanoparticles in Multidrug-Resistant Triple-Negative Breast Cancer by Inhibiting P-Glycoprotein', *Pharmaceutics*, vol. 15, no. 12, p. 2703, Dec. 2023, doi: 10.3390/PHARMACEUTICS15122703/S1.

[87] S. J. Park, J.-H. Son, T.-W. Kong, S.-J. Chang, and H. S. Kim, 'Effect of high-dose polymeric nanoparticle micellar paclitaxel on improved progression-free survival in patients with optimally resected stage III or IV high-grade carcinoma of the ovary: a prospective cohort study with historical controls', *Front Oncol*, vol. 14, p. 1203129, Feb. 2024, doi: 10.3389/fonc.2024.1203129.

[88] M.-D. Zhao *et al.*, 'Co-Delivery of Curcumin and Paclitaxel by "Core-Shell" Targeting Amphiphilic Copolymer to Reverse Resistance in the Treatment of Ovarian Cancer.', *Int J Nanomedicine*, vol. 14, pp. 9453–9467, Dec. 2019, doi: 10.2147/IJN.S224579.

[89] L. Zhang *et al.*, 'Systemic Delivery of Aptamer-Conjugated XBP1 siRNA Nanoparticles for Efficient Suppression of HER2+ Breast Cancer', *ACS Appl Mater Interfaces*, vol. 12, no. 29, pp. 32360–32371, Jul. 2020, doi: 10.1021/acsami.0c07353.

[90] P. Pandey *et al.*, 'An Updated Review on the Nanocarriers Based Co-Delivery System of Chemo Drug Doxorubicin and Phytocompounds', *Polym Adv Technol*, vol. 36, no. 1, p. e70050, Jan. 2025, doi: 10.1002/pat.70050.

[91] A. Figueiras *et al.*, 'New Advances in Biomedical Application of Polymeric Micelles', *Pharmaceutics*, vol. 14, no. 8, p. 1700, Aug. 2022, doi: 10.3390/pharmaceutics14081700.

[92] Y. Chen, H. Zhang, X. Cai, J. Ji, S. He, and G. Zhai, 'Multifunctional mesoporous silica nanocarriers for stimuli-responsive target delivery of anticancer drugs', *RSC Adv*, vol. 6, no. 94, pp. 92073–92091, Sep. 2016, doi: 10.1039/C6RA18062K.

[93] G. Bashiri, M. S. Padilla, K. L. Swingle, S. J. Shepherd, M. J. Mitchell, and K. Wang, 'Nanoparticle protein corona: from structure and function to therapeutic targeting', *Lab Chip*, vol. 23, no. 6, pp. 1432–1466, Mar. 2023, doi: 10.1039/D2LC00799A.

[94] M. Barz, W. J. Parak, and R. Zentel, 'Concepts and Approaches to Reduce or Avoid Protein Corona Formation on Nanoparticles: Challenges and Opportunities', *Advanced Science*, vol. 11, no. 34, p. 2402935, Jul. 2024, doi: 10.1002/advs.202402935.

[95] N. Desai, D. Rana, M. Patel, N. Bajwa, R. Prasad, and L. K. Vora, 'Nanoparticle Therapeutics in Clinical Perspective: Classification, Marketed Products, and Regulatory Landscape', *Small*, p. 2502315, Jun. 2025, doi: 10.1002/smll.202502315.

[96] B. Nejati *et al.*, 'Cancer-on-chip: a breakthrough organ-on-a-chip technology in cancer cell modeling', *Med Biol Eng Comput*, vol. 63, no. 2, pp. 321–337, Feb. 2025, doi: 10.1007/s11517-024-03199-5.

[97] A. Żuchowska, P. Baranowska, M. Flont, Z. Brzózka, and E. Jastrzębska, 'Review: 3D cell models for organ-on-a-chip applications', *Anal Chim Acta*, vol. 1301, p. 342413, May 2024, doi: 10.1016/j.aca.2024.342413.
[98] I. M. Gonçalves *et al.*, 'Organ-on-a-Chip Platforms for Drug Screening and Delivery in Tumor Cells: A Systematic Review', *Cancers (Basel)*, vol. 14, no. 4, p. 935, Feb. 2022, doi: 10.3390/cancers14040935.