**Abstract**

Multidrug resistance (MDR), which significantly decreases the efficacy of anticancer drugs and causes tumor recurrence, has been a major challenge in clinical cancer treatment with chemotherapeutic drugs for decades. Several mechanisms of overcoming drug resistance have been postulated. Well known P-glycoprotein (P-gp) and other drug efflux transporters are considered to be critical in pumping anticancer drugs out of cells and causing chemotherapy failure. Innovative theranostic (therapeutic and diagnostic) strategies with nanoparticles are rapidly evolving and are anticipated to offer opportunities to overcome these limits. In this review, we discuss the mechanisms of drug efflux-mediated resistance and the application of multiple nanoparticle-based platforms to overcome chemoresistance and improve therapeutic outcome.

**Key words** multidrug resistance, drug efflux transporter, cancer nanotechnology

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According to the Global Cancer Report issued by the World Health Organization (WHO), there are over 10 million new cases of cancer each year and over 7.9 million annual deaths from the disease[1]. Serious toxicity is a critical problem for effective chemotherapy because most anticancer agents lack selective efficacy in tumors. Another vital issue is the development of tumor resistance to conventional chemotherapy. Drug resistance, which allows tumors to evade chemotherapeutic agents, has emerged as a major obstacle that limits the efficacy of chemotherapy. The formidable side effects of individual or combined anticancer agents as well as the treatment history and clinical status of the patient must be considered to circumvent the tumor resistance to chemotherapy in clinic. Tumors generally develop significant resistance to repeated treatment with one kind of anticancer agent and then often become resistant to similar or completely different drugs. This mechanism for tumor survival under chemotherapeutic treatment is known as multidrug resistance (MDR). MDR can be intrinsic or acquired through chemotherapeutic drug exposure, and multiple mechanisms are likely to contribute to clinical MDR. Historically, the most significant discovery about MDR was the identification of P-glycoprotein (P-gp)[2], which is overexpressed on the plasma membrane of cancer cells with MDR. Following P-gp, other transporters, such as multidrug resistance-associated protein 1 (MRP1)[3] and multixenobiotic resistance (MXR)[4], are also recognized to relate with drug efflux. In recent years, applications of nanotechnology have shown great promise, with several kinds of nanomedicine entering clinical studies. Although the feasibility and efficacy of reversing drug resistance has been confirmed in vitro and in vivo, the mechanisms by which to use nanotechnology to circumvent this phenotype have not been clarified or fully explored.

This article introduces nanotechnology-based formulations and possible nanomedical approaches to address MDR in tumors, with a specific focus on the use of nanotechnology in cancer to overcome drug efflux-mediated resistance.

**Possible Mechanisms of Drug Efflux-mediated Resistance in Cancer**

The changes that drive antitumor drug resistance
include the following: increased activity of drug efflux pump, such as the ATP-binding cassette (ABC) superfamily; decreased drug influx; activation of DNA repair; metabolic modification or detoxification; and altered expression of apoptosis-associated protein Bcl-2 and tumor suppressor protein p53. Of these mechanisms, overexpression of ABC transporters is the most frequent. ABC transport molecules are generally expressed on the plasma membrane and on the membranes of cellular vesicles, and they play vital physiologic functions and also affect the pharmacokinetic properties of chemotherapeutics in humans. ABC transporters are transmembrane proteins that use the energy of ATP hydrolysis to shuttle various substrates across the cell membrane. To date, there are 48 known transporters in the ABC family, which are classified into seven different subfamilies (ABC A through ABC G) (Table 1). Thirteen ABC transporters contribute to tumor MDR, including P-gp (MDR1/ABCB1), multidrug resistance proteins (MRPs/ABCCs), and breast cancer resistance protein (BCRP/ABCG2), all of which are the most characterized ABC transporters. The normal function of ABC transporters as pumps is to extrude toxins and foreign substances out of the cell. P-gp is the best-known membrane pump molecule of the ABC transporters involved in MDR. Human P-gp, a 170 kDa membrane-associated protein containing 1280 amino acids, is able to carry out an ATP-dependent conformational change that moves the intracellular substrates to the exterior of the cell. It can transport a broad range of structurally related or unrelated compounds including anticancer drugs out of cells and thereby decrease intracellular accumulation of these compounds. Therefore, P-gp expression can physiologically prevent cytotoxic compounds by pump them out of cells to reduce their intracellular concentration. In patients with tumors, P-gp can efflux various anticancer drugs such as doxorubicin and paclitaxel out of cancer cells. Overexpression of P-gp is a common feature of most acquired MDR in solid tumors. Other transporters such as MRP1, MRP2, and BCRP also contribute to drug distribution in the human body in cases where P-gp expression is not significantly altered after treatment.

Application of Nanoparticle Delivery Systems to Reverse Drug Efflux-mediated Resistance

As mentioned above, overexpression of ABC transporters is the broadly known tumor survival mechanism that limits the efficacy of chemotherapeutic agents in clinical cancer treatments. Currently, there are no traditional strategies without serious side effects to completely reverse chemotherapeutic resistance in tumors. Based on their unique physical and biological properties, cancer nanotechnologies developed in recent years offer an unprecedented opportunity for rational delivery of anticancer drugs to solid tumors. The promise of nanotechnology lies in the ability to engineer customizable nanoscale constructs, which have more controllable surface for different modification, and to accommodate multiple types of payloads, such as cancer chemotherapeutics, chemosensitizers, or molecular imaging agents. Nanoparticles have been developed to prevent, detect, and treat resistant cancer cells while minimizing serious toxicity in normal cells and improving drug solubility and stability. Nanostructure platforms derive their effectiveness from adequate delivery systems, including polymers, dendrimers, nanoshells, nanotubes, micelles, liposomes, lipid-based nanoparticles, magnetic nanoparticles, and virus nanoparticles. For rigid nanoparticles, the size to support long circulation in vivo may not exceed 200 nm, a size that is not achievable with individual molecules alone or with equivalent materials at a larger scale. Nanoscale drug delivery systems in the size range of 10–100 nm penetrate preferentially through the tumor vasculature via the so-called enhanced permeability and retention (EPR) effect. Multifunctionalization of hydrophilic nanoparticles can provide a long circulating half-life and prolong the exposure time of chemotherapeutic drugs. These unique properties based on nanostructure effectively increase the intracellular accumulation of anticancer drugs by controllable and efficient release at targeted regions due to their size effect. Furthermore, properly designed nanoparticles with a targeting element can aim at specific targeting sites actively with the therapeutic payloads to overcome tumor MDR. One example is the use of folate acid as an active target. Nanoparticle with folate acid ligands can bind to folate receptors, which were found to be overexpressed on the surface of drug-resistant tumor cells, to achieve the specific accumulation in tumors. In addition, nanoplatforms offer opportunities to coencapsulate multiple therapeutic agents into a single functional carrier and allow imaging to be combined with drug treatment to monitor therapeutic effects in real time. Efforts to co-administrate drugs with ultrasound and thermosensitive therapy or photodynamic therapy improve the nanoparticle delivery systems for synergistic and comprehensive functions of cancer nanotherapy. In summary, the advantages of nanoparticle-based drug delivery system include narrow size distribution, low carrier toxicity, enhanced drug solubilization via protecting drugs from efflux, prevention from drug metabolism or excretion before accumulating in tumors, increased drug loading, prolonged drug circulation, specific site targeting, and controlled drug delivery.
| Gene   | Alias | Subfamily | Location | Gene size (bp) | dN/dS | Transcript | Protein | Main tissue expression | Function                                      | Disease                                      |
|--------|-------|-----------|----------|---------------|--------|------------|---------|------------------------|-----------------------------------------------|-----------------------------------------------|
| ABCA1  | ABC1  | ABC1      | 9q31.1   | 147154        | 0.078  | 1          | 1       | Ubiquitous             | Cholesterol efflux onto HDL drug resistance | Tangier’s disease, familial hypoapo-proteinemia |
| ABCA2  | ABC2  | ABC1      | 9q34.3   | 21689         | 0.043  | 2          | 2       | Brain                  | Drug resistance                               |                                               |
| ABCA3  | ABC3, ABC | 16p13.3 | 53974   | 0.072         | 0.069  | 1          | 1       | Lung                   | Phospholipid metabolism                       | Surfactant deficiency in newborns             |
| ABCA4  | ABCR  | ABC1      | 1p21.3   | 128287        | 0.151  | 1          | 1       | Photoreceptors         | N-retinylidene-PE efflux                      |                                               |
| ABCA5  | ABC1  | ABC1      | 17q24.3  | 80499         | 0.132  | 2          | 2       | Muscle, heart, testes  |                                               |                                               |
| ABCA6  | ABC1  | ABC1      | 17q24.3  | 63169         | 0.356  | 1          | 1       | Liver                  |                                               |                                               |
| ABCA7  | ABC1  | ABC1      | 19p13.3  | 10347         | 0.118  | 2          | 2       | Spleen, thymus        |                                               |                                               |
| ABCA8  | ABC1  | ABC1      | 17q24.3  | 88101         | 0.256  | 1          | 1       | Ovary, heart, skeletal muscle, liver |                                               |                                               |
| ABCA9  | ABC1  | ABC1      | 17q24.3  | 86155         | 0.239  | 2          | 2       | Heart                  |                                               |                                               |
| ABCA10 | ABC1  | ABC1      | 17q24.3  | 96008         | 0.245  | 1          | 1       | Muscle, heart          |                                               |                                               |
| ABCA12 | ABC1  | ABC1      | 2q34     | 206885        | 0.113  | 2          | 2       | Stomach                | Glucosylceramide, other epidermal lipids      | Lamellar ichthyosis type 2 (mild); Harlequin ichthyosis (severe) |
| ABCA13 | ABC1  | ABC1      | 7p12.3   | 449249        | 0.397  | 1          | 1       | Low in all tissues     |                                               |                                               |
| ABCB1  | MDR   | MDR       | 7p21.12  | 209617        | 0.180  | 1          | 1       | Adrenal, kidney, brain, liver, intestine, testis, gland, uterus, ovary | Multidrug resistance                         | Ivermectin sensitivity, digoxin uptake       |
| ABCB2  | MDR   | MDR       | 6p21     | 8765          | 0.016  | 1          | 1       | All cell               | Peptide transport                            | Immune deficiency                            |
| ABCB3  | MDR   | MDR       | 6p21     | 16912         | 0.225  | 2          | 2       | All cell               | Peptide transport                            | Immune deficiency                            |
| ABCB4  | MDR   | MDR       | 7q21.12  | 75506         | 0.152  | 3          | 3       | Liver                  | PC transport                                  | Progressive familial intrahepatic cholestasis–3, intrahepatic cholestasis of pregnancy |
| ABCB5  | MDR   | MDR       | 7p21.1   | 108203        | 0.283  | 1          | 1       | Ubiquitous             |                                               |                                               |
| ABCB6  | MDR   | MDR       | 2q35     | 9179          | 0.201  | 1          | 1       | Mitochondria           | Iron transport                               | Unknown                                      |
| ABCB7  | MDR   | MDR       | Xi q21–22 | 103026        | 0.215  | 1           | 1       | Mitochondria           | Fe/S cluster transport                        | X-linked sideroblastosis and anemia          |
| ABCB8  | MDR   | MDR       | 7q36.1   | 17116         | 0.135  | 1          | 1       | Mitochondria           |                                               |                                               |
| ABCB9  | MDR   | MDR       | 12q24.31 | 46214         | 0.045  | 4          | 3       | Liver                  |                                               |                                               |
| ABCB10 | MDR   | MDR       | 1q42.13  | 42113         | 0.100  | 1          | 1       | Mitochondria           |                                               |                                               |

(To be continued)
| Gene       | Alias     | Subfamily | Location    | Gene size (bp) | dN/dS | Dog  | Mouse | Rat  | Transcript | Protein                  | Main tissue expression | Function                      | Disease                          |
|------------|-----------|-----------|-------------|----------------|--------|------|-------|------|-------------|--------------------------|--------------------------|--------------------------------|
| ABCB11     | SPGP or BSEP | MDR       | 2q24.3      | 108385         | 0.173  | 0.212|       |      | 1           | Liver, intestine          | Bile salt transport        | Progressive familial intrahepatic cholestasis-2 |
| ABCC1      | MRP1      | CF/MRP    | 16p13.12    | 192840         | 0.064  | 0.060| 0.062 |      | 7           | Lung, testes, intestine, PBMC, kidney, brain | Drug resistance          |                               |
| ABCC2      | MRP2 or cMOAT | CF/MRP   | 10q24.2     | 69011          | 0.313  | 0.243| 0.180 |      | 1           | Liver, intestine, kidney | Organic anion efflux       | Dubin-Johnson syndrome     |
| ABCC3      | MRP3      | CF/MRP    | 17q21.33    | 56836          | 0.169  | 0.164| 0.204 |      | 1           | Lung, intestine, liver, kidney, placenta, pancreas, colon | Drug resistance          |                               |
| ABCC4      | MRP4      | CF/MRP    | 13q32.1     | 281594         | 0.137  | 0.099| 0.060 |      | 1           | Prostate, lung, adrenal gland, ovary, testis | Nucleoside transport    |                               |
| ABCC5      | MRP5      | CF/MRP    | 3q27.1      | 97956          | 0.069  | 0.073| 0.053 |      | 1           | Ubiquitous                | Nucleoside transport      |                               |
| ABCC6      | MRP6      | CF/MRP    | 16p13.12    | 73325          | 0.098  | 0.149| 0.160 |      | 1           | Kidney, liver             | Nucleoside transport      | Pseudoxanthoma elasticum  |
| CFTR       | ABCC7     | CF/MRP    | 7q31.31     | 188699         | 0.172  | 0.172| 0.238 |      | 1           | Exocrine tissue           | Chloride ion channel      | Cystic fibrosis CBAVD, pancreatitis, bronchiectasis |
| ABCC8      | SUR1      | CF/MRP    | 11p15.1     | 84017          | 0.093  | 0.045| 0.055 |      | 1           | Pancreas                  | Sulfonylurea receptor     | Familial persistent hyperinsulinemic hypoglycemia of infancy; AD type 2 diabetes |
| ABCC9      | SUR2      | CF/MRP    | 12p12.1     | 135631         | 0.021  | 0.039|       |      | 3           | Heart, muscle             | Regulatory subunit of cardiac K(ATP) channel | Dilated cardiomyopathy with ventricular tachycardia |
| ABCC10     | MRP7      | CF/MRP    | 6q21.1      | 18675          | 0.170  | 0.195| 0.171 |      | 1           | Low in all tissues; a little higher in heart, skeletal muscle, spleen, liver |                               |
| ABCC11     | MRP8      | CF/MRP    | 16q12.1     | 68267          | 0.304  | NA   | NA    |      | 2           | Low in all tissues, a little higher in breast, and testis |                               |
| ABCC12     | MRP9      | CF/MRP    | 16q12.1     | 63798          | 0.200  | 0.184| 0.166 |      | 1           | Low in all tissues, a little higher in breast, testis, brain, ovary, skeletal muscle |                               |
| ABCC13     | ALDP      | ALD       | Xq28        | 19846          | 0.045  | 0.053| 0.058 |      | 1           | Peroxisomes               | VLCFA transport regulation | Adrenoleukodystrophy        |

(To be continued)
Table 1. Demographic and clinical characteristics of the studied population (continued)

| Gene | Alias | Subfamily | Location | Gene size (bp) | dN/dS | Transcript | Protein | Main tissue expression | Function | Disease |
|------|-------|-----------|----------|---------------|--------|------------|---------|------------------------|----------|---------|
| ABCD2 | ALDL1, ALDR | ALD | 12q11 | 67424 | 0.085 | 0.066 | 0.073 | 1 | 1 | Peroxisomes |
| ABCD3 | PXMP1, PMP70 | ALD | 1p22.1 | 100072 | 0.050 | 0.051 | 0.058 | 1 | 1 | Peroxisomes |
| ABCD4 | PMP69, P70R | ALD | 14q24.3 | 17540 | 0.188 | 0.112 | 0.110 | 1 | 1 | Peroxisomes |
| ABCE1 | OABP | OABP | 4p31.31 | 30681 | 0.003 | 0.061 | 0.002 | 1 | 1 | Ovary, testes, spleen |
| ABCF1 | ABC50 | GCN20 | 6p21.1 | 19920 | 0.022 | 0.057 | 0.055 | 1 | 1 | Ubiquitous |
| ABCF2 | GCN20 | 7q36.1 | 19395 | 0.036 | 0.011 | 0.010 | 2 | 2 | Ubiquitous |
| ABCF3 | GCN20 | 3q27.1 | 7908 | 0.027 | 0.030 | 0.035 | 1 | 1 | Ubiquitous |
| ABCG1 | ABC8, ABCG1 | White | 21q22.3 | 97556 | 0.012 | 0.012 | 0.010 | 7 | 7 | Ubiquitous |
| ABCG2 | ABCP, MXR, BCRP | White | 4q22 | 66883 | 0.269 | 0.206 | 0.202 | 1 | 1 | Placenta, intestine, brain |
| ABCG4 | White2 | White | 11q23 | 13626 | 0.026 | 0.064 | 0.027 | 1 | 1 | Liver |
| ABCG5 | White3 | White | 2p21 | 97348 | 0.302 | 0.175 | 0.157 | 1 | 1 | Liver, intestine, Sterol transport, Sitosterolemia |
| ABCG8 | White | White | 2p21 | 39503 | 0.152 | 0.126 | 0.206 | 1 | 1 | Liver, intestine, Sterol transport, Sitosterolemia |

ABC, ATP-binding cassette; HDL, high-density lipoprotein; PGY, P-glucoprotein; MDR, multidrug resistance; MXR, multixenobiotic resistance; MRP, multidrug resistance-associated protein; BCRP, breast cancer resistance protein; TAP, transporter ATP-binding cassette, ATP-binding cassette sub-family B; PC, phosphatidylcholine; MTABC, mitochondrial ATP-binding cassette; SPOC, sister of P-glucoprotein; BSEP, bile salt export pump; MRP, multiple drug resistance protein; PMBMC, peripheral blood mononuclear cell; eMOAT, canalicular multispecific organic anion transporter 1; CF, cystic fibrosis; SUR, sulfonlurea receptor; ALD, adrenoleukodystrophy; ALDP, adrenoleukodystrophy protein; ALDR, adrenoleukodystrophy-related protein; PXMP, peroxisomal membrane protein; PMP, putative peroxisomal membrane protein; OABP, ATP-binding cassette, sub-family F; CBAVD, congenital bilateral absence of the vas deferens; VLCFA, very long chain fatty acid.

Cancer Nanomedicine for Overcoming Drug Efflux-mediated Resistance

An important prerequisite for reversing drug resistance in cancer is achieving a high concentration of the drug in the plasma, a high concentration and long retention time in MDR cancer cells to ensure effective intracellular accumulation. Considering different mechanisms of drug resistance in cancer, nanoparticles are always designed to inhibit or bypass efflux pumps on the membrane or to enhance endocytosis when recognizing MDR tumors. Over 50% of the anticancer drugs used in the clinic today are targeted by P-gp[31]. However, P-gp inhibitors do not have specific selectivity and also block the normal function of P-gp. Nanotechnology refines the concept of co-administering anticancer agents and P-gp inhibitors by combining them into a single drug carrier for simultaneous delivery into MDR tumor cells. In a recent review by Gottesman et al.[32], the strategies for circumventing P-gp-mediated MDR are eloquently categorized as follows: using P-gp inhibitors to block the efflux of cytotoxic agents; using drugs that are not substrates of P-gp; and exploiting the properties of MDR cells, such as receptor overexpression and collateral drug sensitivity. D-alpha-tocopherol polyethylene glycol 1000 succinate (TPGS 1000), which functions as an effective inhibitor of P-gp, turned out to be one of the prominent surfactants that enhancing the cytotoxicity of doxorubicin, vinblastine, paclitaxel, and colchicines in G185 cells comparable to that in the parental cells. Reversal of P-gp activity was due to the effect of TPGS 1000 on transport at concentrations even below its critical micelle point of 0.02 wt%. This excipient was evaluated in a phase II clinical trial for drug resistance[33]. Pluronic block copolymer (P85) is another important and promising example of a modifying agent for P-gp. Membrane fluidization by P85 treatment led to inhibition of the P-gp ATPase drug efflux system and to interference with metabolic processes. These results indicate that both energy depletion (via decreasing ATP pool necessary for P-gp function) and increased permeability and fluidization of a broad spectrum of drugs are critical factors contributing to the activity of the block copolymer for MDR reversion[34,35]. First-generation
agents (for example, the calcium channel blocker verapamil) are limited by unacceptable toxicity to normal tissues, whereas second-generation agents (for example, valspodar and biricodar) have better tolerability but are limited by nonspecificity. Third-generation inhibitors (for example, tariquidar XR9576, LY335979, GF120918, 9576, etc.) have high potency and specificity for P-gp. Tariquidar has shown marked effectiveness in early clinical trials. GF120918 has achieved adequate P-gp inhibition in vivo without significant side effects [36,37].

Taken together, the development of these findings suggests the necessity to consider to combine nanoparticle therapies with P-gp inhibitors. Recent studies also demonstrated that nucleic acid (DNA, miRNA, siRNA, etc.)-based nanoparticles play a critical role in the modulation of drug resistance in tumors by effectively decreasing MDR1 expression in vivo [38-40]. The employed system, which uses siRNA to silence the expression of ABC transporters in combination with an appropriate anticancer drug, is a systemic administration strategy for MDR cells. Meng et al. [40] successfully achieved dual delivery of doxorubicin (Dox) and P-gp siRNA loaded in mesoporous silica nanoparticles (MSNPs). P-gp gene knockdown by siRNA effectively increased the intracellular and intranuclear drug concentration. Similar results were also observed in vitro and in vivo using RGD peptide (arginine-glycine-aspartic acid)-modified liposomes containing P-gp siRNA or doxorubicin [41], MacDiarmid et al. [43] provided a dual sequential treatment strategy for drug-resistant tumors with targeted micelles containing siRNA and a cytotoxic drug. First, the resistant tumors were treated with siRNA/shRNA-containing micelles targeted to tumors via bispecific antibodies (BsAb) for 48 h (for siRNA-containing micelles) and 144 h (for shRNA-containing micelles) to achieve substantial knockdown of MDR1. A second wave of treatment with siRNA/shRNA-containing micelles was followed with intravenous administration of BsAb-targeted micelles packaged with cytotoxic drugs to resistant tumor xenografts. Both the sequential and simultaneous approaches were effective and feasible and markedly decreased the doses of cytotoxic drug necessary for eliminating tumors. Injection of anti-MDR1 short hairpin RNA-encoding vectors into tumor cells with intravenous administration of doxorubicin completely reversed the MDR phenotype and inhibited tumor growth [44].

In addition, some nanomedicines that circumvent
MDR in cancer through other targets are being tested in clinical trials (Table 2). These include taxane analogs DJ-927 (phase II) [51,52] and ortaxel (phase II) [53,54], as well as BMS-184476 (phase II) [55,56] and RPR 109881A (phase I) [57,58], which were purported to have a broad spectrum of activity both in sensitive and resistant tumor cell lines. Nab-paclitaxel is a novel clinical entity incorporating paclitaxel into an albumin nanoparticle, leading to increased intratumoral concentration and showing with superior response rate, longer time to tumor progression, and prolonged survival as second-line therapy in patients with gynecologic cancers, showing with superior response rate, longer time to tumor progression, and prolonged survival as second-line therapy in patients with gynecologic cancers [59,60]. EGFR-targeted polymer-blend nanocarriers with a combination of paclitaxel and lonidamine were found to enhance the therapeutic index of both drugs by inhibiting the Warburg effect and promoting mitochondrial binding of pro-apoptotic Bcl-2 protein (via lonidamine), while hyperstabilizing microtubules (via paclitaxel) [61].

**Future Perspectives**

MDR is a major impediment to the success of cancer chemotherapy. P-gp is the best known membrane transporter involved in MDR in tumors. Several strategies have been used to address MDR, especially P-gp-mediated drug resistance in tumors. However, clinical success has been limited, largely due to lack of efficacy and/or significant toxicity. To overcome both the dose-limiting side effects of conventional chemotherapeutic agents and the therapeutic failure resulting from MDR, cancer nanotechnology has been developed and shown its ability to target tumors based on their unique physical and biological properties. To date, nanoparticles have been investigated primarily to address P-gp and have been shown to improve anticancer efficacy, indicating that nanomedical strategies might provide a new opportunity to overcome MDR [62]. The most predominant advantage of nanomedicine is to deliver and concentrate drugs at the plasma membrane where ABC transporters are located and saturated with extra drugs. In addition, functionalized nanoparticles themselves or their metabolites can also block the function of ABC transporters such as P-gp by direct or indirect interaction and inhibition. The flexibility of nanoparticles with regard to their size and shape increases their potential to enhance drug-loading capacity, stabilize drugs and regulate their release rates, and deliver drugs to targeted sites effectively and specifically. This article provides a glimpse into the nanotechnology-based strategies being developed to overcome drug resistance. To the best of

| Nanotransporters | Main bioactive element | Main Mechanism | Reference |
|-----------------|------------------------|---------------|-----------|
| siRNA, minicells | Doxorubicin | P-gp inhibition | [43] |
| Dendrimer phthalocyanine-encapsulated polymeric micelle (DPC/m)-mediated PCI | Doxorubicin | P-gp inhibition | [45] |
| Poly(D,L-lactide-co-glycolide) | Paclitaxel, tarquidar | P-gp inhibition | [46] |
| Poly(D,L-lactide-co-glyco-lide) nanoparticles | Paclitaxel, P-gp targeted siRNA | P-gp inhibition | [47] |
| Albumin bound nanoparticles | Paclitaxel | Paclitaxel-induced NF-κB pathway that up-regulates VEGF-A | [48] |
| Aerosol-OT (AOT) | Doxorubicin | Prevents the accumulation of anticancer drugs | [49,50] |
| Folate receptor-targeting nanoparticle | Heparin-folate-paclitaxel (HFT) backbone with an additional paclitaxel | P-gp inhibition | [51] |
| PLGA nanoparticles | Vincristine sulfate, verapamil hydrochloride | Enhanced permeation and retention effect | [52] |
| Cationic liposome-polycation-DNA (LPD) and anionic liposome-polycation-DNA (LPD-II) | Doxorubicin and siRNA | Avoid P-gp efflux and increase Dox uptake | [53] |
| Polymer-blend nanoparticle | Ceramide | Modulation of the apoptotic threshold | [54] |
| Albumin bound nanoparticles | Rapamycin and perifosine | Suppression of the PI3K/Akt/mTOR pathway | [55] |
| Fe(3)O(4)-magnetic nanoparticle | Daunorubicin | Mdr-1 inhibition | [56] |

P-gp, P-glycoprotein; aerosol-OT (AOT), bis-2-ethylhexyloxyl sodium sulfosuccinate; PLGA, poly(lactic-co-glycolic acid); VEGF-A, vascular endothelial growth factor A; Dox, doxorubicin; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; mTOR, mammalian target of rapamycin; Mdr-1, multidrug resistant gene-1.
our knowledge, however, there are currently no nano-formulations for drug delivery aimed at overcoming drug resistance that have been effective in clinical tests. Various nanocarriers for targeted delivery of anticancer drugs have already undergone in vivo testing in mouse models (Table 2) and clinical evaluation in humans. With better understanding of the physiologic properties of drug-resistant tumors and enhanced nanomaterial design, there will be more opportunities to develop multifunctional nanomaterials for circumventing drug resistance. A safe and effective multifunctional nanosystem could provide a versatile platform to benefit patients with MDR tumors in the future.

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