

Plasma Glycoprotein Efflux Induced Resistance: Implications, Mechanism, Inhibitors, and Novel Strategies to Overcome

Chenmala Karthika, Raman Sureshkumar, U. V. Shivasaraun, C. Vasanthi, P. Nethravathi

Department of Pharmaceutics, JSS College of Pharmacy, Ooty, Tamil Nadu, India

Abstract

This review aims at the drug-resistant factors, its effects, and methods to overcome. P-glycoprotein (P-gp) is an energy-dependent efflux transporter which plays a leading role in multidrug resistance (MDR) of the majority of drugs and is involved in the efflux of toxins, xenobiotics, and drugs out of the body. Their unique mechanism of action put them in the spotlight for the drug discovery process. Modification of drug transporters through inhibitors, inducers or the methods of genetic polymorphism are being used recently. Uses of specific inhibitors or blockers with a parent drug have been evolved as a new method to alter MDR. These inhibitors are classified into various generations based on the properties that they exhibit. MDR is a significant obstacle resulting from the overexpression of some proteins like P-gp which reduces therapeutic efficacy of various drugs associated with cancer, tuberculosis, malaria, and human immunodeficiency virus, etc. Inhibitors of P-gp can be regarded as an explicit remedy for this puzzling condition. Although various chemical inhibitors had been developed, natural agents are comparatively safer than synthetic or semi-synthetic agents. Novel strategies and formulations are developed to alter the expression of P-gp is also mentioned in this paper.

Key words: Multidrug resistance, natural inhibitors, P-glycoprotein inhibitors, P-glycoprotein substrate, P-glycoprotein

INTRODUCTION

Drug resistance is defined as a decline in the efficacy of a medicament such as in antineoplastic or antimicrobial therapy and its reduction in the curing of a disease or a condition.^[1] Drug resistance will create challenges in therapeutic efficacy of the drug and in conducting further research to tackle them. When an organism acquires tolerance to more than one drug, it is referred to as multidrug resistance (MDR). Long-term treatment followed by the repeated use of medicament may cause reduced pharmacological action in patients. Increasing the dose also cannot produce any significant effect in this situation.^[2] If the human becomes resistant to a drug, then it is known as drug tolerance. Two types of drug tolerance are usually seen: Pharmacokinetic tolerance and pharmacodynamics drug tolerance.

Pharmacokinetic or metabolic tolerance

The drug that enters into our body is first absorbed into the bloodstream, which then

transports and distributes the drug into various sites; where it disintegrates into smaller segments, and eventually gets excreted from the body. All these factors influence the duration of action, potency and side effects of the drug. Pharmacokinetic tolerance mainly occurs when there is a substantial decrease in the amount of drug that reaches the target site. This can be caused by a significant increase in the secretion of enzymes required for the degradation of drugs, for example, cytochrome P450 (CYP450) enzymes. This type of tolerance is mainly noticed in the oral administration of the drug which causes first pass metabolism. Enzyme induction is one of the main reasons for drug resistance and various

Address for correspondence:

Raman Sureshkumar,
Department of Pharmaceutics,
JSS College of Pharmacy, (A Constituent College of JSS
Academy of Higher Education, Mysuru), Rocklands,
The Nilgiris, Ootacamund, Ooty, Tamil Nadu – 643 001,
India. Tel.: +91-9865064872. Fax: 91-423-2442937.
E-mail: sureshcoonoor@yahoo.com

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other factors and mechanisms also play a key role in drug resistance which is discussed in detail in this paper.

Pharmacodynamic tolerance

Pharmacodynamic tolerance develops when the cellular reaction to a substance is reduced eventually. A leading cause of pharmacodynamic tolerance is an increase in the concentration of a substrate that binds constantly with a receptor leading to desensitization of the receptor.^[3] Other priorities include a decrease in the receptor density which mainly occurs in association with receptor agonist or other possibilities causing an alteration in the action potential firing rate. In most of the cases, the resistance will occur after continuous exposure to a drug, but instant tolerance can also occur in some cases.^[4]

FACTORS RESPONSIBLE FOR DRUG RESISTANCE

There are various types of drug resistance such as antibiotic resistance, anticancer resistance, antitubercular drug resistance, anti-human immunodeficiency virus (HIV) drug resistance, antimicrobial resistance, and antimalarial drug resistance. Most of the drug resistance have been caused by MDR proteins. P-glycoprotein (P-gp) being one among those proteins plays a major aspect in decreasing the drug efficacy in most of the treatments. P-gp is a transmembrane (TM) glycoprotein physiologically expressed in cell types such as in liver, kidney, pancreas, jejunum,^[5] and colon; it also shows its expression in brain capillary endothelial cells also. The main role of P-gp includes protection of cells from the entry of xenobiotics and toxic substances. Due to its expression in the diseased cells, its inhibition is needed for the success of the therapy.

TRANSPORTERS AND ITS FAMILY

P-gp is an efflux system belonging to MDR1 or ATP binding cassette (ABC) sub-family B member 1 or cluster of differentiation 243 which belongs to ABCB (MDR) superfamily of ABC transporters.^[6] ABC gene represents the largest family of TM protein, found mostly in the plasma membrane or intracellular membrane. The energy-driven from ATP helps in the transport of these molecules across the cell membrane. 49 ABC transporters are identified,^[7] in humans. MDR1A, MDR1B, and MDR2^[8] are found in animals. In humans two classes of P-gp gene family-MDR1 and MDR3 exists,^[9] where MDR1 or P-gp is often seen in all parts of the body and expels a range of drugs over the plasma membrane, while MDR3 or P-gp is mostly seen in liver in the canalicular membranes of hepatocytes and is responsible for the phosphatidylcholine secretion into the bile.^[10] Even though the crisis of MDR3 or P-gp in the transport of the

drug has been proven recently, they are not involved directly in drug resistance.

P-gp carries greater pharmacological importance by preventing the influx of toxic substances and xenobiotics into placenta, brain, and gonads by elimination through the intestinal lumen, brain, and urine. It is significantly involved in many drug interactions.^[11] P-gp efflux the amphipathic drugs with the help of energy driven from ATP hydrolysis.

P-gp has seen in the body parts such as intestine, kidney, testis, liver,^[12] and brain.^[13] P-gp is localized in the luminal membrane of endothelial cells of the blood capillaries where it prevents the entry of xenobiotics. Overexpression of P-gp is a major cause of MDR in various treatments and a crucial factor in the failure of chemotherapy. P-gp overexpression also causes drug resistance to antidepressants, anti-epileptics,^[14] and anti-HIV medicines. P-gp related studies are performed in rats,^[15] mice, and humans.^[16] The substrates that merge with P-gp have an extraneous framework. The compounds transported by P-gp are treated as substrates, while compounds that accord the role of transporter are considered as inhibitors.

P-gp was characterized first in 1976 in Chinese hamster ovary cells, where it was determined to exhibit resistance to anticancer drugs.^[17] P-gp was found to be responsible for conferring resistance to cytotoxic drugs. Researchers had shown that radioactive verapamil can be used for measuring P-gp functions using positron emission tomography.^[18] P-gp is utilized for separating transitional B-cells from native B-cells. Dyes such as Rhodamine 123 and Mito Tracker Dyes are used for this purpose.^[19]

CELLULAR LOCALIZATION

The expression of P-gp is frequently found higher in the cancer cells, causing MDR by efflux of hydrophobic drugs from the cell. In human tumors, P-gp is expressed in colon, renal, and adrenal carcinomas; rarely in lungs and germ cell tumors and certain gastric carcinomas; and is undetectable in endometrial carcinomas and breast. In normal cells, the concentration of the P-gp usually found is low, but certain cell type in the kidney, colon, liver, pancreas, and jejunum provides an ideal location for P-gp. In liver, P-gp is broadly distributed on the biliary canalicular front of hepatocytes and on the apical surface of epithelial cells in small biliary ductules. When it comes in the case of pancreas, P-gp is exclusively determined on the apical surface of epithelial cells of the small ductules. In kidney, it is mostly found on the apical surface of epithelial cells of the proximal tubule.^[5] Both colon and jejunum show the identical level in the apical surface of superficial columnar epithelial cells. In the adrenal glands highly distributed amount of P-gp is seen on the surface of both medulla and cortex cells.^[20] Its presence is also found in specialized epithelial cells for both secretory and excretory functions, trophoblast in^[21] placenta,

and in endothelial cells of capillary blood vessels at blood-tissue barrier sites. It is also found in the epithelium of gastrointestinal tract and bronchi, salivary gland, prostate gland, and sebaceous glands of the skin. Evidence showed that the presence of P-gp in the human fetus is having an importance in the normal functioning of various organs in the early phases of embryo development.^[22] Studies which had conducted in humans^[23] and rodent^[5] tissues shown that explicit level of protein in the normal tissue is low and found to be much higher at the apical surface of epithelial cells lining the colon, small intestine, pancreatic ductules, bile ductules, kidney proximal tubules, and adrenal glands.^[24] Expression of P-gp is seen higher at the luminal surface of secretory epithelial cells in the pregnant endothelium as well as in placenta^[25] where it protects the fetus.

P-GP AND ITS KINETICS

Absorption

The major cause of MDR is due to P-gp. P-gp transports an ample range of pharmacological and anatomically distinct cytotoxic compounds from the cell by its membrane-bound drug efflux pump. Inhibition of P-gp has become a decisive approach for overcoming MDR in cancer cells. Co-administration of P-gp inhibitors can alter this issue. Not only with cancer treatment but also P-gp driven MDR is observed in other disease conditions.^[26] Overexpression of P-gp by diseased cells other than the normal cells is a major cause of the resistance of drugs to various diseases. Researchers have revealed that P-gp plays a crucial part in the antibiotic resistance. P-gp trims the overall permeability of drug to the targeted site by reducing the bioavailability.^[27]

Distribution

When it comes to the distribution of the drugs P-gp is an integral element of biological barriers such as blood-brain barrier (BBB) and placental barrier. It can significantly impact the distribution of various therapeutic agents. P-gp efflux transporters in the BBB avert various neurotoxic elements from penetrating the brain thus ultimately limiting the central distribution of drugs that are used for central nervous system (CNS) diseases.^[28] The inhibition of P-gp efflux transporter at BBB forms a novel approach for overcoming drug resistance to CNS diseases. P-gp significantly causes drug resistance in Parkinson's and Alzheimer's disease.^[29,30] P-gp restricts the access of various potentially toxic and foreign bodies from entering into fetus through the placenta, hence considered as a game changer in the placental protective mechanism.^[31]

Metabolism

The major reason for the decrease in bioavailability and therapeutic efficacy of drugs administered through oral route are P-gp drug efflux and biotransformation by intestinal

mediated CYP3A4 enzymes. These are the major defense system in our intestine, protecting from harmful drugs and xenobiotics which usually serves as the main substrate for proteins which, in turn, results in a low bioavailability of drugs absorbed through the oral route. These proteins are mostly expressed in hepatocytes and enterocytes and contribute their role in first pass metabolism of drugs and specificity of binding of drugs with these proteins will overlap to an extent.

For example, piperine is a natural inhibitor of the P-gp and CYP3A4 enzyme is found in black pepper increases the plasma concentration of various drugs which acts as a substrate for these proteins when co-administered.^[32] Grapefruit juice also acts by this mechanism; it can act as an inhibitor for these proteins and can increase the therapeutic efficacy of saquinavir and many other drugs by increasing the plasma level concentration when the drug is administered through the oral route.

Elimination

Renal excretion

The mechanism of renal excretion is the function of glomerular filtration, tubular secretion, and reabsorption.^[33] P-gp forms a trans-epithelial pathway for drug transport, where xenobiotics and drugs get eliminated through the urine from our body. This is also a major cause of the decrease in plasma concentration of the drug in our body. When Cyclosporine A and digoxin is co-administered, cyclosporine will alter the excretion of digoxin by trans-epithelial pathway by increasing the plasma concentration of digoxin and decreasing the rate of glomerular filtration and tubular secretion.^[34] Similar kind of action is observed when cimetidine and itraconazole are co-administered.^[35]

Biliary excretion

P-gp mediated biliary excretion and clearance of the drugs can be reduced to an extent using these inhibitors. Quercetin, an inhibitor of P-gp alters the therapeutic efficacy of various drugs when in combination. Drugs such as Azithromycin, doxorubicin, cyclosporine A, and erythromycin have an inhibitory effect on biliary excretion of drugs mediated by P-gp.^[36]

MECHANISM OF DRUG RESISTANCE

The four mechanisms by which microorganisms exhibit resistance to antimicrobial drugs are as follows:

- Drug modification or inactivation: For example, production of β -lactamase and the enzymatic deactivation of penicillin G in some bacteria which are penicillin resistant.
- Target site variation: The penicillin-binding site PBP is shifted in MRSA and other penicillin-resistant bacteria.

- Modification of metabolic pathway: For example, the para-aminobenzoic acid pathway is not required for the sulfonamide resistant bacteria which are the substantial precursor for the synthesis of nucleic acid and folic acid, instead of like mammalian cells they utilize preformed folic acid.
- Reduction in intercellular drug concentration: Drug accumulation inside the cells is reduced by decreasing the drug permeability and a decrease in drug influx across the cell surface.

Role of P-gp in drug resistance

P-gp leads a major role in regulating the distribution and bioavailability of drugs where P-gp increases the expression in intestine and reduces the absorption of drug which acts as a substrate of P-gp. Therefore, bioavailability and therapeutic plasma concentration of the drug is not attained. However, when the P-gp expression is reduced, the drug will reach suprathreshold plasma concentration causing drug toxicity.^[9]

The substrate enters into P-gp through an opening at the cytoplasmic side of protein or by an opening in the inner leaflet of the membrane. ATP will bind at the cytoplasmic side of the protein. Followed by its binding, ATP hydrolysis alters the substrate which is to be removed from the cell. When phosphate is released from the native ATP molecule, the substrate will get excreted. A new molecule of ATP binds to the secondary ATP binding site when adenosine diphosphate (ADP) is released. This process will restart again when the hydrolysis and discharge of ADP and a phosphate molecule reboot the protein. This mechanism is been depicted in Figure 1.

P-GP SUBSTRATE

P-gp transports an ample variety of substrate with a distinct chemical structure. P-gp substrate generally appears to be hydrophobic and amphipathic.^[37,38] The drugs which usually act as P-gp substrate are mentioned in Table 1.

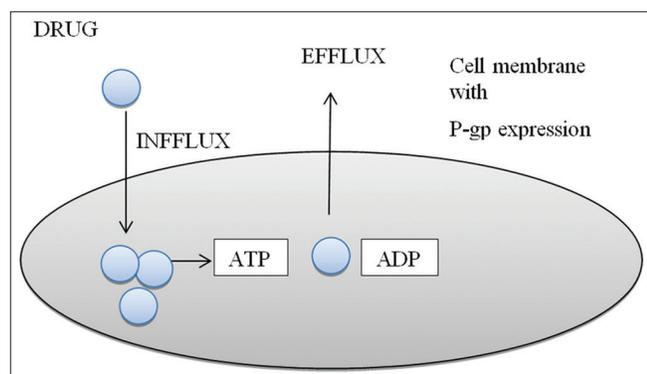


Figure 1: Mechanism of drug efflux by plasma glycoprotein

The inhibition of P-gp can be made possible by two mechanisms either competition of drug binding sites without interrupting the ATP hydrolysis or blockage of the ATP hydrolysis process.^[39] Recently, a new mechanism by inhibition of P-gp mediated drug transport by an allosteric mechanism is proposed.^[40] P-gp substrates are usually lipophilic and connect with the proteins within the membrane before being either expelled into the extracellular aqueous phase or moved to the extracellular membrane leaflets. P-gp substrate involves various drugs that are clinically utilized in the treatment of diseases in humans, and the protein which is present in the luminal surface of the intestine shows a leading role in *in vivo* drug absorption and distribution. Using potent inducer of P-gp and CYP450, pharmacokinetic properties of risperidone can be altered.^[41]

P-GP INHIBITION

Evidences proved that P-gp is able to interact with >20 substrate or modulators. Substrates that are directly transported by P-gp include vinca alkaloids, anthracycline, and fluorescent lipids. The binding of modulators such as verapamil and cyclosporine which blocks the transporter activity can be significantly applicable in chemotherapy. The drug binding pockets of P-gp are highly flexible with low specificity, hence, can overcome MDR development of more potent modulators or inhibitors is needed. P-gp inhibitors are generally categorized based on their toxicity, affinity, and specificity. Inhibitors or modulators which are capable of reversing MDR are generally divided into three. Examples of inhibitors are listed in Table 2.

Table 1: List of P-gp substrates

| Category | Drugs |
|----------------------|---|
| Antineoplastic drugs | Cisplatin, daunorubicin, Actinomycin, doxorubicin, cyclosporine-A, docetaxel, etoposide, mitomycin-C, irinotecan, imatinib mitoxantrone, paclitaxel, teniposide, vincristine, and Vinblastine |
| Cardiovascular drugs | Quinidine, bunitrolol, diltiazem, digitoxin, losartan, celiprolol, digoxin, lovastatin, talinolol, and atorvastatin |
| Antiviral drugs | Nelfinavir, saquinavir, ritonavir, indinavir, and amprenavir |
| GIT drugs | Domperidone, loperamide, Cimetidine, ondansetron, and risperidone |
| Others | Chloroquine, colchicines, fexofenadine, morphine, dexamethasone, tacrolimus, phenytoin, etc |

P-gp: P-glycoprotein, GIT: Gastrointestinal tract

Table 2: List of P-gp inhibitors

| Generations | Examples |
|------------------------------|--|
| First generation inhibitors | Verapamil, cyclosporine A, reserpine, quinidine, yohimbine, tamoxifen, and toremifene |
| Second generation inhibitors | Doxverapamil, valspodar, biricodar citrate, dextriguldipine, and dofequidar fumerate |
| Third generation inhibitors | Tariquidar, zosuquidr, laniquidar, elacridar, mitotane, annamycin, biricodar, ONT-093, R10933, and HM30181 |
| Natural inhibitors | Curcumin, piperine, capsaicin, and [6]-gingerol, carnosic acid, limonin, quercetin, β -carotene, leutolin, and anthocynine |

P-gp: P-glycoprotein

First generation MDR transporter inhibitors

They are pharmacologically active substances; which inhibits P-gp and also used for specific treatment. These include verapamil, cyclosporine A, reserpine, quinidine, yohimbine, tamoxifen, and toremifene. In leukemia cells; drug resistance could be reversed by verapamil^[42] for the effective inhibition; higher doses are given to the patients which, in turn, causes cardiovascular toxicity.^[43] These inhibitors are restricted due to their low therapeutic response; hence, these are replaced by the second generation inhibitors.

Second generation MDR transporter inhibitors

These are pharmacologically inactive substances but exhibit their action on P-gp. Second generation MDR transporters are designed by structurally modifying first generation to obtain low cell toxicity, high specificity, and potency. Examples include doxverapamil,^[44] valspodar (PSC 833),^[45] biricodar citrate (VX710),^[46] dextriguldipine, and dofequidar fumerate. Second generation MDR transporters mainly includes non-immunosuppressive analogs of cyclosporine A and dox verapamil. However, most frequently used inhibitor is PSC 833 which is 5–10 times more potent than cyclosporine A.^[47] However, these transporters have the greater affinity and inhibit both CYP4 enzymes and also other ABC transporters.

Third generation MDR inhibitors

For overcoming the problems faced by first two generations; the third generation of MDR transporter inhibitors is developed. These minimize the demerits of the other two generation and are highly specific and effective against P-gp with minimal toxic effects. These inhibitors possess no pharmacokinetic interactions with other two generation and

are highly specific and effective against P-gp with minimal toxicity. They do not exhibit pharmacokinetic interaction with other chemotherapeutic drugs and compared with the first and second generation inhibitors; these are more than 200 fold potent in reversing MDR. Examples include Tariquidar (XR9576), Zosuquidar (LY335979),^[48] Laniquidar (R101933),^[49] Elacridar (F12091),^[50] Mitotane (NSC-38721),^[51] annamycin,^[52] R10933,^[53] Biricodar, ONT-093, and HM30181. QSAR and 3D QSAR studies found that the structure of these inhibitors is responsible for their modulating functions. 32 Anthranilamide derivatives of tariquidar study results have proved that the hydrophobic domain is required for inhibitory functions, which includes aromatic ring system and a heteroatom near the Anthranilamide nucleus at the other end of tetrahydroquinoline group. Recent studies have shown that tariquidar has both substrate and inhibitory effect on P-gp.^[54,55]

NATURAL INHIBITORS

Due to toxicity and limited therapeutic efficacy of synthetic inhibitors, new research studies have been developed, which include natural products and dietary supplements. Food extracts and natural compounds are discovered with an effect on P-gp which, in turn, reverses MDR.

Spices

From the ancient period onward spices are used as a coloring agent and also as preservatives. Various research studies had shown that the phytochemicals present in spices play a leading role in the inhibition, cure of diseases and P-gp reversal and management of MDR.^[56]

Curcumin

Curcumin is used as anti-inflammatory, antioxidant, anti-infection, and anticancer treatment,^[57] it also has an additional use as it reverses MDR caused by P-gp. It inhibits P-gp by P13K/Akt/NF-kB^[58] pathway in MDR leukemia L1210 cells of the mouse. Choi *et al.*, in 2008, proved that when Adriamycin and curcumin are given in combination, western blotting results clearly show that it can cause the cleavage of PARP and it can overcome MDR caused by P-gp.^[59] Curcumin loaded mucoadhesive microemulsion can be effectively targeted to the brain through intranasal route.^[60]

Piperine

Piperine, a major alkaloid in black pepper, is consumed by the majority of populations in the world. Later studies proved that Piperine could inhibit MDR through ABC transporter inhibitor.^[61] mRNA which expresses MDR1, ABCC, and ABCG2 encoding P-gp has been inhibited by piperine.

Capsaicin

Capsaicin which is found in red chili exhibit anticancer activity, it exhibits inhibition of P-gp and potentiates the anticancer activity of vinblastine, over P-gp modulation.^[62] It inhibits NF-KB and β -catenin pathway.

[6]-Gingerol

[6]-Gingerol is an important phytochemical constituent present in ginger, which provides its spicy taste. It also inhibits NF-KB and β -catenine pathway like capsaicin, but the actual mechanism of action is not well known.^[63]

Carnosic acid

Carnosic acid is a major phenolic derivative present in the leaves of rosemary, containing 20% of this compound. These leaves are used as a spice for cooking. Studies had shown that Carnosic acid might be a P-gp substrate, where it stimulates the ATP activity of P-gp, by it competitively binds to the ATP binding site.^[64]

Grape seed procyanidine

This polyphenolic compound is highly found in grape seeds and also in fruits vegetables and tea leaves. It possesses both antiproliferative and chemopreventive activity.^[65] Studies revealed that it inhibits NF-KB and translocate YB-1 into the nucleus through dephosphorylation of ERK1/2 and AKT.^[66]

Limonin

Citrus foods are highly rich in this white crystalline compound. It inhibits P-gp^[67] in colon, leukemia, and melanoma cell lines. It enhances intracellular accumulation of doxorubicin and Rhodamine 123, which, in turn, in a concentration of 20 μ m enhances the anticancer activity of doxorubicin in CED/ADR5000 leukemia cells and Caco-2 colon cells.

Quercetin

A flavonoid found abundantly in apple and onion. Using experimental models, quercetin is found to be a good chemosensitizer and inhibiting P-gp expression and its activity. At a very low concentration of 0.7 μ M itself, it can increase the anticancer activity of doxorubicin and acts against MCF-7 breast carcinoma.^[68]

β -Carotene

β -Carotene found in vegetables and fruits including pumpkin, carrot, and sweet potato and is a precursor of Vitamin A.^[69] In Caco-2 cells, it stimulates the efficacy of doxorubicin,

etoposide, and 5-fluorouracil and it even hampers the P-gp transport activity.

Fruits and vegetables

Evidence says that increased consumption of fruits and vegetables will decrease the risk of cancer and other diseases.^[70] The mode of action depends on the presence of the phytochemical constituents found in fruits and vegetables.

APPROACHES FOR OVERCOMING MDR

Various new strategies were developed to overcome the MDR in cells such as physical, biological, and chemical methods as well as nanotechnologies^[71] ribonucleic acid (RNA) interference and micro RNA. MicroRNAs are small non-coding RNAs that bind to the 3'UTR of mRNA and hinder the delivery of protein at the translational level. Micro RNAs are typically not regulated in cancer cells, and modification in miRNA level may lead to the development of MDR. To hamper the expression of P-gp various sequence of miRNAs such miR-27a, -296, -298, -451, and -1253 were determined, and their effects were found in breast cancer cells and esophageal carcinoma cells.^[72] To find out the mechanism of miRNA effect on drug resistance, miRNAs series of vincristine were carried out on resistance, and sensitive colon cells in association with 24 miRNA showing significance divergent, 17 of them show significance in drug resistance cells. These miRNAs can be utilized as a biomarker for cancer treatment and diagnosis. Synthetic siRNA is also used for the overcoming the resistance by inhibiting the outcomes associated with MDR genes.^[73] For example increase in the sensitivity and potent increase in the cell proliferation of chemotherapeutic drugs in drug-resistant gastric cancer cells by reducing the expression of ABCC4 with the use of RNA interference.^[74]

Monoclonal antibodies to overcome MDR

In the early 1980s, two monoclonal antibodies were discovered to target the resistance which is developed by P-gp both *in vitro* and *in vivo*.^[75] MRK-16 inhibited vincristine and actinomycin-D efflux while the proliferation of MDR cells is inhibited by MRK-17. Anticancer activity can be enhanced by conjugating the monoclonal antibodies with p-gp inhibiting agents. UIC2 a mouse monoclonal antibody was developed by Echetner Roninson, recognized as an extracellular part to which P-gp binds. UIC2 increases the influx of P-gp substrates and eventually increases the cytotoxicity of P-gp substrates, where no effects are identified with other anti-P-gp antibody.^[76]

Development of non-substrate

Since anticancer drugs are showing MDR in cancer cells, then new anticancer drugs are developed, which are less recognized by the P-gp or other ABC transporters. For example,

BMS-184476,^[77] ortataxel, and taxane^[78] analogs DJ-927 are not recognized by P-gp. Pharmacokinetic interaction takes place between CYP450 enzyme 3A4, P-gp modulators as most of the first and second generation inhibitors of P-gp acts as a substrate of CYP450 enzyme 3A4.^[43]

Nanotechnology and MDR

Nanoparticles are widely used to deliver anti-inflammation, anti-infective, and antitumor drugs. These are in the size range of 1–100 nm. Types of nanoparticles include solid lipid, metals, liposomes, micelles, dendrimers, polymers, and quantum dots^[79,80] assembly of nanoparticles are of multi-layered and the coating of the particles are made to overcome the problems related to stability, solubility, and specificity.^[81] The complications associated with macromolecules such as low specificity, high dose, cell toxicity, and cellular uptake can be minimized by loading the nanoparticles with the drug, which can even overcome the issues related with resistant part of P-gp.^[82] Comparing with freely diffusing lipophilic drugs, nanoparticles loaded with drugs have characteristics to overcome MDR and enhancement of therapeutic value. In spite of this approach combination of the drugs are also developed such as anticancer drugs and P-gp inhibitors to overcome the resistance.

Liposomes

Liposomes are substantially used for the delivery of the drugs which are impotent of diffusion over membrane layers. These can form micelle spheres and phospholipid bilayers that can encapsulate soluble drugs and can retain their natural activity. Thus, nanoparticles exhibit convincing activity in reversing MDR. For example, Doxil (PEG-liposomal doxorubicin) exhibits antitumor in mice with doxorubicin-resistant C26 or colon cancer C26 tumor models.^[83] In addition with Doxil, various other drugs in association with liposomal nanoparticles had discovered to hamper MDR in cancer cells.

Micelles

Polymeric micelles are core-shell nanostructures containing both lipophilic and lipophobic blocks are used to load lipophilic drugs in the core.^[84] Lipophobic block allows the solubilization of lipophilic drugs and even protects the drug from degradation. Thus, micelle-based delivery system has long circulation in the blood, also reverses P-gp mediated drug efflux. Through a self-emulsifying drug delivery system with the use of the bio-enhancer excipients, the pharmacokinetic properties of the drug fexofenadine can be increased by blocking the P-gp and CYP450 mechanisms.

Mesoporous silica nanoparticles

Mesoporous silica materials (MSNPS) have large pore volume, large pore size, and high surface area and are

biocompatible in nature. MSNPS can load both siRNA and antitumor drugs at the same time.^[85] Codelivery of two antitumor drugs can hamper the resistance caused by P-gp and can increase the therapeutic efficacy of the drugs.^[86]

Polymeric nanoparticles

Polymers used are mostly biodegradable and are natural or synthetic in nature. Chitosan, gelatine, and albumin (protein) are natural polymers included and poly {D, L-lactic acid}, poly {ε-caprolactone}, and poly {D, L-lactic acid} are synthetic in nature.^[87] Techniques which are used for polymeric nanoparticles are dialysis, salting out, interfacial polymerization, microemulsion, supercritical fluid technique, and solvent evaporation. Human albumin nanoparticles of paclitaxel and abraxane are formed to improve the efficacy for metastatic pancreatic and breast cancer.^[88] This formulation is approved by US Food and Drug Administration for its clinical use. Cisplatin is a platinum-based drug used in the treatment of various cancers in the trade name of Platinol. However, its utility is diminished by its adverse effects and resistance. This problem associated with resistance can be overcome using PEGylated nanoparticle. Which minimizes the dose of the cisplatin and effectively delivers the drug to the cancer cell.^[89]

CONCLUSION

P-gp is important in various aspects such as a protective biological barrier by excluding toxins, drugs, and xenobiotics from brain and fetal cells. On the other hand, it is having an impact on the MDR in various diseased conditions. It's also interfering in the pharmacological profile of various drugs in humans. Overcoming the MDR became a decisive approach to the drug development. The inhibition of P-gp is also a crucial step because long-term inhibition leads to ineffectiveness in pharmacological functioning and retaining its action will be difficult. P-gp protects from the attack of toxins and foreign bodies from invading into the body cells. These also act as a barrier against the drugs and its metabolites from entry into the cells, hence, provided with its negative feedback. Hence, the handling with P-gp should be very careful as its inhibition may also provide a negative impact on the body.

REFERENCES

1. Lowe HJ, Barnett GO. Understanding and using the medical subject headings (MeSH) vocabulary to perform literature searches. *JAMA* 1994;271:1103-8.
2. Miller NS, Dackis CA, Gold MS. The relationship of addiction, tolerance, and dependence to alcohol and drugs: A neurochemical approach. *J Subst Abuse Treat* 1987;4:197-207.
3. Bespalov A, Müller R, Relo AL, Hudzik T. Drug tolerance:

- A known unknown in translational neuroscience. *Trends Pharmacol Sci* 2016;37:364-78.
4. Swanson J, Gupta S, Guinta D, Flynn D, Agler D, Lerner M, *et al.* Acute tolerance to methylphenidate in the treatment of attention deficit hyperactivity disorder in children. *Clin Pharmacol Ther* 1999;66:295-305.
 5. Thiebaut F, Tsuruo T, Hamada H, Gottesman MM, Pastan I, Willingham MC, *et al.* Cellular localization of the multidrug-resistance gene product P-glycoprotein in normal human tissues. *Proc Natl Acad Sci U S A* 1987;84:7735-8.
 6. Vishal R, Tandon B, Kapoor G, Bano S, Gupta Z, Gillani S, *et al.* P-glycoprotein pharmacological relevance. *Indian Pharmacol* 2006;38:13-24.
 7. Dean M, Rzhetsky A, Allikmets R. The human ATP-binding cassette (ABC) transporter superfamily. *Genome Res* 2001;11:1156-66.
 8. Fischer V, Einolf HJ, Cohen D. Efflux transporters and their clinical relevance. *Mini Rev Med Chem* 2005;5:183-95.
 9. Lin JH, Yamazaki M. Role of P-glycoprotein in pharmacokinetics: Clinical implications. *Clin Pharmacokinet* 2003;42:59-98.
 10. van Helvoort A, Smith AJ, Sprong H, Fritzsche I, Schinkel AH, Borst P, *et al.* MDR1 P-glycoprotein is a lipid translocase of broad specificity, while MDR3 P-glycoprotein specifically translocates phosphatidylcholine. *Cell* 1996;87:507-17.
 11. Colabufo NA, Berardi F, Contino M, Niso M, Perrone R. ABC pumps and their role in active drug transport. *Curr Top Med Chem* 2009;9:119-29.
 12. Pérez-Tomás R. Multidrug resistance: Retrospect and prospects in anti-cancer drug treatment. *Curr Med Chem* 2006;13:1859-76.
 13. Ohtsuki S, Terasaki T. Contribution of carrier-mediated transport systems to the blood-brain barrier as a supporting and protecting interface for the brain; Importance for CNS drug discovery and development. *Pharm Res* 2007;24:1745-58.
 14. Lazarowski A, Czornyj L, Lubienieki F, Girardi E, Vazquez S, D'Giano C, *et al.* ABC transporters during epilepsy and mechanisms underlying multidrug resistance in refractory epilepsy. *Epilepsia* 2007;48 Suppl 5:140-9.
 15. Syvänen S, Hooker A, Rahman O, Wilking H, Blomquist G, Långström B, *et al.* Pharmacokinetics of P-glycoprotein inhibition in the rat blood-brain barrier. *J Pharm Sci* 2008;97:5386-400.
 16. Ikoma Y, Takano A, Ito H, Kusuhara H, Sugiyama Y, Arakawa R, *et al.* Quantitative analysis of ¹¹C-verapamil transfer at the human blood-brain barrier for evaluation of P-glycoprotein function. *J Nucl Med* 2006;47:1531-7.
 17. Juliano RL, Ling V. A surface glycoprotein modulating drug permeability in Chinese hamster ovary cell mutants. *Biochim Biophys Acta* 1976;455:152-62.
 18. Luurtsema G, Windhorst AD, Mooijer MP, Herscheid JD, Lammertsma AA, Franssen EJ. Fully automated high yield synthesis of (R)- and (S)-[¹¹C] verapamil for measuring P-glycoprotein function with positron emission tomography. *J Label Compd Radiopharm* 2002;45:1199-207.
 19. Wirths S, Lanzavecchia A. ABCB1 transporter discriminates human resting naive B cells from cycling transitional and memory B cells. *Eur J Immunol* 2005;35:3433-41.
 20. Croop JM, Raymond M, Haber D, Devault A, Arceci RJ, Gros P, *et al.* The three mouse multidrug resistance (mdr) genes are expressed in a tissue-specific manner in normal mouse tissues. *Mol Cell Biol* 1989;9:1346-50.
 21. Arceci RJ, Croop JM, Horwitz SB, Housman D. The gene encoding multidrug resistance is induced and expressed at high levels during pregnancy in the secretory epithelium of the uterus. *Proc Natl Acad Sci U S A* 1988;85:4350-4.
 22. Marzolini C, Kim RB. Placental transfer of antiretroviral drugs. *Clin Pharmacol Ther* 2005;78:118-22.
 23. Cordon-Cardo C, O'Brien JP, Boccia J, Casals D, Bertino JR, Melamed MR, *et al.* Expression of the multidrug resistance gene product (P-glycoprotein) in human normal and tumor tissues. *J Histochem Cytochem* 1990;38:1277-87.
 24. van der Valk P, van Kalken CK, Ketelaars H, Broxterman HJ, Scheffer G, Kuiper CM, *et al.* Distribution of multi-drug resistance-associated P-glycoprotein in normal and neoplastic human tissues. Analysis with 3 monoclonal antibodies recognizing different epitopes of the P-glycoprotein molecule. *Ann Oncol* 1990;1:56-64.
 25. van Kalken CK, Giaccone G, van der Valk P, Kuiper CM, Hadisaputro MM, Bosma SA, *et al.* Multidrug resistance gene (P-glycoprotein) expression in the human fetus. *Am J Pathol* 1992;141:1063-72.
 26. Breedveld P, Pluim D, Cipriani G, Wielinga P, van Tellingen O, Schinkel AH, *et al.* The effect of bcrp1 (Abcg2) on the *in vivo* pharmacokinetics and brain penetration of imatinib mesylate (Gleevec): Implications for the use of breast cancer resistance protein and P-glycoprotein inhibitors to enable the brain penetration of imatinib in patients. *Cancer Res* 2005;65:2577-82.
 27. Mullin S, Mani N, Grossman TH. Inhibition of antibiotic efflux in bacteria by the novel multidrug resistance inhibitors biricodar (VX-710) and timcodar (VX-853). *Antimicrob Agents Chemother* 2004;48:4171-6.
 28. Löscher W, Potschka H. Blood-brain barrier active efflux transporters: ATP-binding cassette gene family. *NeuroRx* 2005;2:86-98.
 29. Kwan P, Brodie MJ. Potential role of drug transporters in the pathogenesis of medically intractable epilepsy. *Epilepsia* 2005;46:224-35.
 30. Kortekaas R, Leenders KL, van Oostrom JC, Vaalburg W, Bart J, Willemsen AT, *et al.* Blood-brain barrier dysfunction in parkinsonian midbrain *in vivo*. *Ann Neurol* 2005;57:176-9.
 31. Syme MR, Paxton JW, Keelan JA. Drug transfer and

- metabolism by the human placenta. *Clin Pharmacokinet* 2004;43:487-514.
32. Bhardwaj RK, Glaeser H, Becquemont L, Klotz U, Gupta SK, Fromm MF, *et al.* Piperine, a major constituent of black pepper, inhibits human P-glycoprotein and CYP3A4. *J Pharmacol Exp Ther* 2002;302:645-50.
 33. Fanos V, Cataldi L. Renal transport of antibiotics and nephrotoxicity: A review. *J Antimicrob Chemother* 2001; 13:461-72.
 34. Rengelshausen J, Göggelmann C, Burhenne J, Riedel KD, Ludwig J, Weiss J, *et al.* Contribution of increased oral bioavailability and reduced nonglomerular renal clearance of digoxin to the digoxin-clarithromycin interaction. *Br J Clin Pharmacol* 2003;56:32-8.
 35. Karyekar CS, Eddington ND, Briglia A, Gubbins PO, Dowling TC. Renal interaction between itraconazole and cimetidine. *J Clin Pharmacol* 2004;44:919-27.
 36. Zhao YL, Cai SH, Wang L, Kitaichi K, Tatsumi Y, Nadai M, *et al.* Possible involvement of P-glycoprotein in the biliary excretion of grepafloxacin. *Clin Exp Pharmacol Physiol* 2002;29:167-72.
 37. Schwab M, Eichelbaum M, Fromm MF. Genetic polymorphisms of the human MDR1 drug transporter. *Annu Rev Pharmacol Toxicol* 2003;43:285-307.
 38. Sauna ZE, Ambudkar SV. Evidence for a requirement for ATP hydrolysis at two distinct steps during a single turnover of the catalytic cycle of human P-glycoprotein. *Proc Natl Acad Sci U S A* 2000;97:2515-20.
 39. Sauna ZE, Smith MM, Müller M, Kerr KM, Ambudkar SV. The mechanism of action of multidrug-resistance-linked P-glycoprotein. *J Bioenerg Biomembr* 2001; 33:481-91.
 40. Maki N, Hafkemeyer P, Dey S. Allosteric modulation of human P-glycoprotein. Inhibition of transport by preventing substrate translocation and dissociation. *J Biol Chem* 2003;278:18132-9.
 41. Lee KS, Park JH, Lee HJ, Rhie S. Preclinical study of a potent P-glycoprotein and cytochrome P450 enzyme inducer rifampicin changing pharmacokinetic parameters of risperidone and its metabolite, 9-hydroxyrisperidone, using a rat model. *J Pharm Invest* 2012;42:345-51.
 42. Koski A, Raki M, Nokisalmi P, Liikanen I, Kangasniemi L, Joensuu T, *et al.* Verapamil results in increased blood levels of oncolytic adenovirus in treatment of patients with advanced cancer. *Mol Ther* 2012;20:221-9.
 43. Thomas H, Coley HM. Overcoming multidrug resistance in cancer: An update on the clinical strategy of inhibiting p-glycoprotein. *Cancer Control* 2003;10:159-65.
 44. Wilson WH, Jamis-Dow C, Bryant G, Balis FM, Klecker RW, Bates SE, *et al.* Phase I and pharmacokinetic study of the multidrug resistance modulator dexverapamil with EPOCH chemotherapy. *J Clin Oncol* 1995;13:1985-94.
 45. Tidefelt U, Liliemark J, Gruber A, Liliemark E, Sundman-Engberg B, Juliusson G, *et al.* P-glycoprotein inhibitor valspodar (PSC 833) increases the intracellular concentrations of daunorubicin *in vivo* in patients with P-glycoprotein-positive acute myeloid leukemia. *J Clin Oncol* 2000;18:1837-44.
 46. Minderman H, O'Loughlin KL, Pendyala L, Baer MR. VX-710 (biricodar) increases drug retention and enhances chemosensitivity in resistant cells overexpressing P-glycoprotein, multidrug resistance protein, and breast cancer resistance protein. *Clin Cancer Res* 2004;10:1826-34.
 47. Friche E, Jensen PB, Nissen NI. Comparison of cyclosporin A and SDZ PSC833 as multidrug-resistance modulators in a daunorubicin-resistant Ehrlich ascites tumor. *Cancer Chemother Pharmacol* 1992;30:235-7.
 48. Kemper EM, Cleypool C, Boogerd W, Beijnen JH, van Tellingen O. The influence of the P-glycoprotein inhibitor zosuquidar trihydrochloride (LY335979) on the brain penetration of paclitaxel in mice. *Cancer Chemother Pharmacol* 2004;53:173-8.
 49. Luurtsema G, Schuit RC, Klok RP, Verbeek J, Leysen JE, Lammertsma AA, *et al.* Evaluation of [¹¹C]laniquidar as a tracer of P-glycoprotein: Radiosynthesis and biodistribution in rats. *Nucl Med Biol* 2009;36:643-9.
 50. Dörner B, Kuntner C, Bankstahl JP, Bankstahl M, Stanek J, Wanek T, *et al.* Synthesis and small-animal positron emission tomography evaluation of [¹¹C]-elacridar as a radiotracer to assess the distribution of P-glycoprotein at the blood-brain barrier. *J Med Chem* 2009;52:6073-82.
 51. Bates SE, Shieh CY, Mickley LA, Dichek HL, Gazdar A, Loriaux DL, *et al.* Mitotane enhances cytotoxicity of chemotherapy in cell lines expressing a multidrug resistance gene (mdr-1/P-glycoprotein) which is also expressed by adrenocortical carcinomas. *J Clin Endocrinol Metab* 1991;73:18-29.
 52. Consoli U, Priebe W, Ling YH, Mahadevia R, Griffin M, Zhao S, *et al.* The novel anthracycline annamycin is not affected by P-glycoprotein-related multidrug resistance: Comparison with idarubicin and doxorubicin in HL-60 leukemia cell lines. *Blood* 1996;88:633-44.
 53. van Zuylem L, Sparreboom A, van der Gaast A, van der Burg ME, van Beurden V, Bol CJ, *et al.* The orally administered P-glycoprotein inhibitor R101933 does not alter the plasma pharmacokinetics of docetaxel. *Clin Cancer Res* 2000;6:1365-71.
 54. Pajeva IK, Wiese M. Structure-activity relationships of tariquidar analogs as multidrug resistance modulators. *AAPS J* 2009;11:435-44.
 55. Kannan P, Telu S, Shukla S, Ambudkar SV, Pike VW, Halldin C, *et al.* The "specific" P-glycoprotein inhibitor tariquidar is also a substrate and an inhibitor for breast cancer resistance protein (BCRP/ABCG2). *ACS Chem Neurosci* 2011;2:82-9.
 56. Aggarwal BB, Kunnumakkara AB, Harikumar KB, Tharakan ST, Sung B, Anand P, *et al.* Potential of spice-derived phytochemicals for cancer prevention. *Planta Med* 2008;74:1560-9.
 57. Anuchapreeda S, Leechanachai P, Smith MM, Ambudkar SV, Limtrakul PN. Modulation of P-glycoprotein expression and function by curcumin in multidrug-resistant human KB cells. *Biochem Pharmacol*

- 2002;64:573-82.
58. Choi BH, Kim CG, Lim Y, Shin SY, Lee YH. Curcumin down-regulates the multidrug-resistance *mdr1b* gene by inhibiting the PI3K/Akt/NF kappa B pathway. *Cancer Lett* 2008;259:111-8.
 59. Zhang W, Han Y, Lim SL, Lim LY. Dietary regulation of P-gp function and expression. *Expert Opin Drug Metab Toxicol* 2009;5:789-801.
 60. Mandal SD, Mandal S, Patel J. Brain targeting efficiency of curcumin loaded mucoadhesive microemulsion through intranasal route. *Drug Deliv* 2016;46:179-88.
 61. Bezerra DP, de Castro FO, Alves AP, Pessoa C, de Moraes MO, Silveira ER, *et al.* *In vitro* and *in vivo* antitumor effect of 5-FU combined with piplartine and piperine. *J Appl Toxicol* 2008;28:156-63.
 62. Nabekura T, Kamiyama S, Kitagawa S. Effects of dietary chemopreventive phytochemicals on P-glycoprotein function. *Biochem Biophys Res Commun* 2005; 327:866-70.
 63. Nabekura T. Overcoming multidrug resistance in human cancer cells by natural compounds. *Toxins (Basel)* 2010; 2:1207-24.
 64. Nabekura T, Yamaki T, Hiroi T, Ueno K, Kitagawa S. Inhibition of anticancer drug efflux transporter P-glycoprotein by rosemary phytochemicals. *Pharmacol Res* 2010;61:259-63.
 65. Chen Q, Zhang R, Li WM, Niu YJ, Guo HC, Liu XH, *et al.* The protective effect of grape seed procyanidin extract against cadmium-induced renal oxidative damage in mice. *Environ Toxicol Pharmacol* 2013;36:759-68.
 66. Hsu CP, Lin YH, Chou CC, Zhou SP, Hsu YC, Liu CL, *et al.* Mechanisms of grape seed procyanidin-induced apoptosis in colorectal carcinoma cells. *Anticancer Res* 2009;29:283-9.
 67. Han YL, Yu HL, Li D, Meng XL, Zhou ZY, Yu Q, *et al.* Inhibitory effects of limonin on six human cytochrome P450 enzymes and P-glycoprotein *in vitro*. *Toxicol In Vitro* 2011;25:1828-33.
 68. Borska S, Chmielewska M, Wysocka T, Drag-Zalesinska M, Zabel M, Dziegiel P, *et al.* *In vitro* effect of quercetin on human gastric carcinoma: Targeting cancer cells death and MDR. *Food Chem Toxicol* 2012; 50:3375-83.
 69. Chieli E, Romiti N, Rodeiro I, Garrido G. *In vitro* modulation of ABCB1/P-glycoprotein expression by polyphenols from *Mangifera indica*. *Chem Biol Interact* 2010;186:287-94.
 70. Nile SH, Park SW. Edible berries: Bioactive components and their effect on human health. *Nutrition* 2014;30:134-44.
 71. Livney YD, Assaraf YG. Rationally designed nanovehicles to overcome cancer chemoresistance. *Adv Drug Deliv Rev* 2013;65:1716-30.
 72. Bao L, Hazari S, Mehra S, Kaushal D, Moroz K, Dash S, *et al.* Increased expression of P-glycoprotein and doxorubicin chemoresistance of metastatic breast cancer is regulated by miR-298. *Am J Pathol* 2012; 180:2490-503.
 73. Hong L, Han Y, Zhang H, Li M, Gong T, Sun L, *et al.* The prognostic and chemotherapeutic value of miR-296 in esophageal squamous cell carcinoma. *Ann Surg* 2010;251:1056-63.
 74. Perez J, Bardin C, Rigal C, Anthony B, Rousseau R, Dutour A, *et al.* Anti-MDR1 siRNA restores chemosensitivity in chemoresistant breast carcinoma and osteosarcoma cell lines. *Anticancer Res* 2011;31:2813-20.
 75. Broxterman HJ, Kuiper CM, Schuurhuis GJ, Tsuruo T, Pinedo HM, Lankelma J, *et al.* Increase of daunorubicin and vincristine accumulation in multidrug resistant human ovarian carcinoma cells by a monoclonal antibody reacting with P-glycoprotein. *Biochem Pharmacol* 1988;37:2389-93.
 76. Mechetner EB, Roninson IB. Efficient inhibition of P-glycoprotein-mediated multidrug resistance with a monoclonal antibody. *Proc Natl Acad Sci U S A* 1992;89:5824-8.
 77. Altstadt TJ, Fairchild CR, Golik J, Johnston KA, Kadow JF, Lee FY, *et al.* Synthesis and antitumor activity of novel C-7 paclitaxel ethers: Discovery of BMS-184476. *J Med Chem* 2001;44:4577-83.
 78. Cassinelli G, Lanzi C, Supino R, Pratesi G, Zuco V, Laccabue D, *et al.* Cellular bases of the antitumor activity of the novel taxane IDN 5109 (BAY59-8862) on hormone-refractory prostate cancer. *Clin Cancer Res* 2002;8:2647-54.
 79. Bar-Zeev M, Assaraf YG, Livney YD. B-casein nanovehicles for oral delivery of chemotherapeutic drug combinations overcoming P-glycoprotein-mediated multidrug resistance in human gastric cancer cells. *Oncotarget* 2016;7:23322-34.
 80. Yang L, Li W, Kirberger M, Liao W, Ren J. Design of nanomaterial based systems for novel vaccine development. *Biomater Sci* 2016;4:785-802.
 81. Cho K, Wang X, Nie S, Chen ZG, Shin DM. Therapeutic nanoparticles for drug delivery in cancer. *Clin Cancer Res* 2008;14:1310-6.
 82. Wen Y, Meng WS. Recent *in vivo* evidences of particle-based delivery of small-interfering RNA (siRNA) into solid tumors. *J Pharm Innov* 2014;9:158-73.
 83. Ogawara K, Un K, Tanaka K, Higaki K, Kimura T. *In vivo* anti-tumor effect of PEG liposomal doxorubicin (DOX) in DOX-resistant tumor-bearing mice: Involvement of cytotoxic effect on vascular endothelial cells. *J Control Release* 2009;133:4-10.
 84. Kataoka K, Harada A, Nagasaki Y. Block copolymer micelles for drug delivery: Design, characterization and biological significance. *Adv Drug Deliv Rev* 2001;47:113-31.
 85. Chen AM, Zhang M, Wei D, Stueber D, Taratula O, Minko T, *et al.* Co-delivery of doxorubicin and bcl-2 siRNA by mesoporous silica nanoparticles enhances the efficacy of chemotherapy in multidrug-resistant cancer cells. *Small* 2009;5:2673-7.
 86. Sheng J, Li F, Wong ST. Optimal drug prediction from

- personal genomics profiles. *IEEE J Biomed Health Inform* 2015;19:1264-70.
87. Devulapally R, Paulmurugan R. Polymer nanoparticles for drug and small silencing RNA delivery to treat cancers of different phenotypes. *Wiley Interdiscip Rev Nanomed Nanobiotechnol* 2014;6:40-60.
88. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, *et al.* Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013; 369:1691-703.
89. Dhar S, Gu FX, Langer R, Farokhzad OC, Lippard SJ. Targeted delivery of cisplatin to prostate cancer cells by aptamer functionalized pt(IV) prodrug-PLGA-PEG nanoparticles. *Proc Natl Acad Sci U S A* 2008; 105:17356-61.

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