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Research Article

PLASMA GLYCOPROTEIN INHIBITORS AS A NEW TARGET FOR OPTIMAL DRUG DELIVERY

Alla Narayana Rao*, Y. Bhargav, B. Sai Krishna, M. Prasanna Teja and MSC. Bose

Mother Teresa Pharmacy College, Sathupally, Khammam District, Telangana, India.

ABSTRACT

Plasma glycoprotein (P-gp), a transmembrane permeability glycoprotein, is a member of ATP Binding Cassette (ABC) super family that functions specifically as carrier mediated primary active efflux transporter. It is widely distributed throughout the body and has a diverse range of substrates. Several vital therapeutic agents are substrates to P-gp and their bioavailability is lowered or a resistance is induced because of protein efflux. Hence P-gp inhibitors were explored for overcoming multidrug resistance and poor bioavailability problems of the therapeutic P-gp substrates. This review represents a brief discussion on P-gp mediated drug transport and how it hinders the success of various therapies. Its main focus is on various strategies used to improve the drug delivery and targeting.

Keywords: P-glycoprotein, drug efflux, bioavailability, drug delivery, drug resistance.

INTRODUCTION

P-glycoprotein (P-gp) is one of the first members of the ATP-binding cassette (ABC) transporter which acts as a physiological barrier by extruding toxins and xenobiotics out of cells[1,2]. P-gp is primarily found in epithelial cells which have the excretory roles including apical surface of epithelial cells lining the colon, small intestine, pancreatic ductules, bile ductules, kidney proximal tubules, and the adrenal gland[3-5].It is also located in the endothelial cells of the blood brain barrier (BBB)[6]. The transporter is overexpressed on the surface of many neoplastic cells and restricts cell entry. The role of P-gp is likely to protect these susceptible organs from toxic compounds, preventing them to enter the cytosol and extrude them to the exterior[7].Thus it also enhances the secretion of metabolites and xenobiotics into bile, urine, and the lumen of gastrointestinal tract[1].P-gp in human forms a small gene family with two isoforms. The class I isoform (MDR1/ABCB1) is a drug transporter while the class II isoform (MDR2/3/ABCB4) carries out export of phosphatidylcholine into the bile[2,8].A single P-gp molecule can recognize and transport numerous drugs with a wide range of chemical structures, ranging from a molecular weight of 250 g/mol (cimetidine) to 1202 g/mol (cyclosporin)[9].

Additionally, it has a role in limiting cellular uptake of drugs from blood circulation into the brain while being present in the BBB. P-gp is overexpressed in cancer cells and is responsible for drug efflux in tumors. It prevents cell internalization of chemotherapeutic agents and makes the chemotherapy almost ineffective in many cases. Hence, this protein is one of the main barriers in cancer treatment by chemotherapy[12-13]. A variety of strategies are being developed to overcome the difficulties associated with P-gp in optimum drug delivery. Those include not only inhibition of P-gp, but also various techniques to bypass it[1,4,15,16]. These promising approaches for optimizing drug delivery and targeting will be the focus of discussions in this review.

P-gpSTRUCTURE AND DISTRIBUTION

P-gp is a 170 kDa membrane-bound protein, an energy-dependent efflux transporter driven by ATP hydrolysis. It is composed of two homologous and symmetrical halves (cassettes), each of which contains six transmembrane domains that are separated by an intracellular flexible linker polypeptide loop, approximately 75 amino acids in length with an ATP-binding motif[17].There are two ATP-binding domains of P-gp, located in the cytosol side. ATP-binding

domain(s) are also known as nucleotide-binding folds (NBFs). The NBFs are located in the cytoplasm and they transfer the energy to transport the substrates across the membranes. ABC pumps are mostly unidirectional.

Each ATP-binding domain contains three regions: Walker A, B, and signature C motifs. Highly conserved Lys residue within the walker A motif of histadinepermease is directly involved with the binding of ATP[18]and a highly conserved Asp residue within the walker B motif serves to bind the Mg^{2+}ion. Human P-gp, the MDR1 gene product, requires both $Mg^{(2+)}$-ATP-binding and hydrolysis to function as a drug transporter. It has also been proposed that magnesium may play a role in stabilizing the ATP-binding site[19].Signature C motifs probably participate to accelerate ATP hydrolysis via chemical transition state interaction[20]and is also suggested to be involved in the transduction of the energy of ATP hydrolysis to the conformational changes in the membraneintegral domains required for translocation of the substrate[21].

Each of the two transmembrane domains of P-gp consists of six long α-helical segments.Five of the α-helices from each transmembrane domain are related by a pseudo-twofold symmetry, whereas the sixth breaks the symmetry. The two α-helices positioned closest to the (pseudo)symmetry axis at the center of the molecule appear to be linked[22].P-gp has amino- and carboxyterminals. Initially, it was believed that N-terminal ATP-binding domain contains all residues necessary to hydrolyze ATP without interacting with the C-terminal ATP-binding domain[23].But now it is believed that both the amino- and carboxy-terminal ATP sites can hydrolyze ATP. However, there is no evidence that ATP can be hydrolyzed simultaneously by both sites[24].

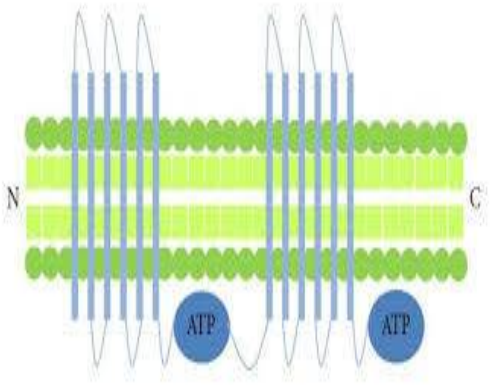

Fig. 1: P-gp Structure

P-gp EXPRESSION IN NORMAL TISSUES

- P-gp has been present in several human normal tissues, including the liver, kidney, pancreas, and small and large intestine[25].
- In all of these organs, P-gp is localized at the luminal surface of epithelial cells,it may have a physiological role in the elimination of xenobiotics or some endogenous metabolites[26-27].
- P-gp is also expressed by endothelial cells at blood-tissue barrier sites, such as the blood-brain barrier and, thus, may protect the brain from circulatingxenobiotics, including anticancer drugs[28].
- P-gp is also expressed in columnar epithelial cells of lower gastrointestinal tract(GIT), capillary endothelial cells of brain and testis, canalicular surface of hepatocytes.
- Due to selective distribution of P-gp at the drug entry and exit ports,P-gp could play a major physiological role in absorption, distribution and excretion of xenobiotics.
- overall P-gp functions as a biochemical barrier for entry of xenobiotics and expels them from the organs into the systemic circulation[29].

P-gp EXPRESSION IN CANCER

- Numerous studies have been conducted during the last few years to analyze the expression of P-gp insolid tumors and haematological malignancies and to determine its clinical relevance.
- P-gp expression is usually high and constitutive in tumors that arise from tissues known to physiologically express the carrier, such as carcinoma of the colon, kidney, adrenal gland, pancreas and liver.
- Intermediate levels of P-gp expression have been observed at time of diagnosis in some neuroblastomas and soft tissue carcinomas and in some haematological malignancies.
- low P-gp expression shows in tumors of the lung, esophagus, stomach, ovary and breast, melanomas, lymphomas, multiple myelomas and some leukemias.
- some of these malignancies may display elevated levels of P-gp after chemotherapy[30].
- A higher incidence of P-gp expression after treatment which incidence to

develops a drug resistance markers due to the expression of Multi-drug resistance associated protein (MRP)[31].

MECHANISM OF P-gp MEDIATED EFFLUX

- The efflux action of the protein follows a carrier mediated primary active transport mechanism.
- In this process, the protein pump export needs direct ATP requirement and the energy released from the ATP hydrolysis gives the driving force for extrusion process.
- The efflux takes place unidirectionally (out of the cells into the extracellular space) and transfers only one molecule at a time. Thus, P-gp is a uniporter carrier protein[34-36].

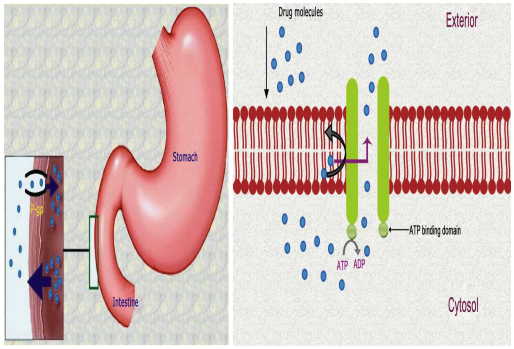

Fig. 2: P-gp Distribution and Efflux Mechanism

CATEGORY OF DRUGS EFFLUX BY P-gp

P-gp can extrude a wide range of structurally diverse compounds out of the cells. Hundreds of substrates (usually hydrophobic) interact with this ATP dependent transporter including anticancer agents, immunosuppressants, steroid hormones, calcium channel blockers, beta-adrenoreceptor blockers, cardiac glycosides, among others[32-33]. Less permeable drugs (weak substrates) may also undergoa substantial extrusion. Thus it contributes greatly in the extrusion of many drugs from the blood into the intestinal lumen.

Anticancer drugs

Actinomycin, cyclosporine-A, cisplatin, daunorubicin, docetaxel, doxorubicin, irinotecan, mitomycin-C, mitoxantrone, paclitaxel, teniposide, vinblastine, etoposide, imatinib and vincristine.

Cardiovascular drugs

Atorvastatin, lovastatin, bunitrolol, celiprolol, talinolol, diltiazem, digoxin, digitoxin, losartan, quinidine, and verapamil.

Antiviral drugs

amprenavir, indinavir, saquinavir, nelfinavir, and ritonavir.

Antibacterial agents

Erythromycin, rifampin, sparfloxacin, levofloxacin, and pazufloxacin.

GIT drugs

Cimetidine, risperidone, domperidone, loperamide and ondansetron.

Others

Chloroquine, colchicines, dexamethasone, fexofenadine, morphine, phenytoin, tacrolimus, etc.

P-gp is also responsible for enhancing the excretion of drugs out of hepatocytes and renal tubules into the adjacent luminal space. Therefore, P-gp can potentially reduce the absorption and oral bioavailability and decrease the retention time of a number of drugs.

INHIBITION OF P-gp

- The inhibition of efflux pump is mainly done in order to improve the delivery of therapeutic agents.
- P-gp can be inhibited by three mechanisms
  (i) Blocking drug binding site either competitively, non-competitively or allosterically
  (ii) Interfering with ATP hydrolysis and
  (iii) Altering integrity of cell membrane lipids.

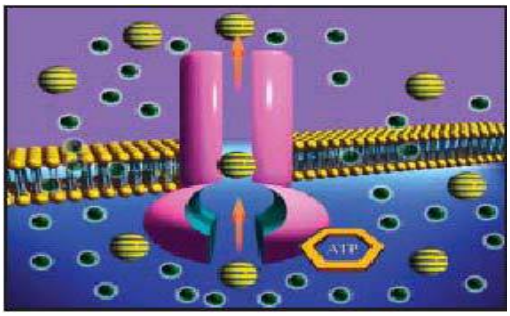

Fig. 3: Competitive inhibition of P-gp

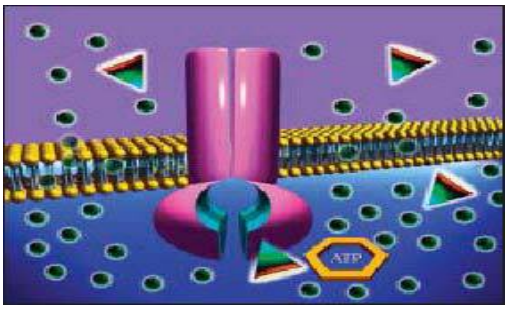

Fig. 4: Noncompetitive inhibition of P-gp

- The main goal is to achieve improved drug bioavailability, uptake of drug in the targeted organ, and more efficacious cancer chemotherapy through the ability to selectively block the action of P-gp.
- P-gp inhibitors are classified into three generations based on their specificity, affinity, and toxicity.

Table 1: Classification and limitations of P-gp Inhibitors

S.No.	Generation	Examples	Specificity	Limitation
1	First generation	Verapamil Cyclosporine A Reserpine Quinidine Yohimbine Tamoxifen Toremifena.	Non-selective and low binding affinities.	They are substrates to other transporters and enzyme systems. They are pharmacologically active. They themselves are transported by P-gp.
2	Second generation	Dexverapamil Dexniguldipine Valspodar (PSC 833) Dofequidarfumarate (MS-209)	Higher specificity then first generation inhibitors but interact with other systems.	They are substrates to CYP 3A4 enzyme and other ABC transporters.
3	Third generation	Zosuquidar (LY335979) Laniquidar (R101933) Mitotane (NSC-38721) Biricodar (VX-710) Elacridar(GF120918/GG918) ONT-093 Tariquidar (XR9576)	Highest specificity that specifically and potently inhibit P-gp function.	No limitations like the first and the second generation inhibitors

FIRST GENERATION P-gp INHIBITORS

First-generation inhibitors are pharmacological compounds, which were developed and are used for other indications but have been shown to inhibit P-gp. Many agents of diverse structure and function that modulate P-gp have been identified. These include calcium channel blockers such as verapamil; immunosuppressants like cyclosporine A; anti-hypertensives, reserpine, quinidine and yohimbine; and antiestrogens like tamoxifen and toremifene. Vincristine inhibited P-gp by 95% and was more potent than other anthracycline analogues tested[37]. First generation compounds tend to be less potent, non-selective and their usage being limited by toxicity due to the high serum concentrations achieved with the dose that is required to inhibit P-gp. In addition, many ofthe first-generation chemosensitizers werethemselves substrates for P-gp and competed withthe co-administered substrates for efflux by the MDR pumps. As a result, high serum concentrations of the chemosensitizers were needed to produce sufficient intracellular concentrations. Clinical trials with first generationMDR drugs failed due to these reasons andconsequently, this prompted researchers and pharmaceutical industries to move in the direction of second and third-generation inhibitors which would specifically modulate P-gp.

SECOND GENERATION P-gp INHIBITORS

Second-generation modulators constitute the agents that lack the pharmacological activity of the first generation compounds and possess a higher P-gp affinity. Examples of agents belonging to this category include PSC 833 (nonimmunosuppresive analogues of cyclosporin A) and dexverapamil (R-isomer of verapamil lacking the cardiac effects), biricodar (VX-710), GF120918 and MS-209 (14, 33). Although these compounds were developed with a view to have less toxicity, still they retained some characteristics that limited their clinical usefulness. The affinity of second-generation MDR drugs towards P-gp was too low to produce significant inhibition in vivo at tolerable doses. Most of the second-generation chemosensitizers were also substrates for CYP 3A4[38]. As a result, the competition between anticancer agents and MDR modulators for CYP

3A4 activity resulted in unpredictable pharmacokinetic interactions affecting the metabolism and/or clearance mechanisms. This produced increased anticancer drug concentrations leading to unacceptable side effects, necessitating dose reductions down to sub-toxic levels. Furthermore, inhibition of non-target transporters by these compounds enhanced adverse effects of anticancer drugs[39].

THIRD GENERATION P-gp INHIBITORS

Structure-activity relationships and combinatorial chemistry approaches have resulted in development of novel third-generation P-gp blockers, primarily with the purpose to improve the treatment of multidrug resistant tumours and to inhibit P-gp with high specificity and toxicity. They are neither metabolized by CYP 3A4 andnor they alter the plasma pharmacokinetics ofanticancer drugs. Modulators such as LY335979,OC144093 and XR9576 are identified to behighly potent (active in nano-molar ranges) andselective inhibitors of P-gp with a potency ofabout 10-fold more than the first and second generationinhibitors[40,41] . None of the third generation agents tested so far have causedclinically relevant alterations in thepharmacokinetics of the co-administeredanticancer drugs. As a result, such compoundsoriginating from various drug developmentprograms offer significant improvements incancer therapy and are currently undergoingclinical trials with various anticancer drugs inseveral types of cancer[38]. Tariquidar(anthranilamide derivative) gave successfulresults in phase I and II studies with paclitaxel and vinorelbine in ovarian cancer, and phase III trials have already been initiated.

USES OF P-gp INHIBITORS

i) Enhancement of Bioavailability and Transport[43-47]

- P-gp inhibitor is co-administered with the drug to enhance drug absorption.
  Ex:HM30181, a newly developed third generation P-gp inhibitor, is co-administration (10 mg/kg) greatly increased oral bioavailability of paclitaxel from **3.4%** to **41.3%** in rats.
- P-gp inhibitors may have a great impact on altering pharmacokinetics of a drug. Since P-gp molecules are present in many organs like BBB, kidney proximal tubule, and bile ductule, their inhibition can potentially improve not only the absorption, but also the distribution, metabolism, and elimination of their substrates
  Ex:Asperen et al observed a 10-fold increased oral bioavailability of paclitaxel in mice administered along with a P-gp blocker (valspodar).
- BBB is considered as the main barrier to prevent drugs entering the central nervous system (CNS). P-gp inhibition can prevent P-gp mediated drug efflux and assist the substrate molecules to enter the CNS.
  Ex:Kemper et al reported a 5-fold increase in brain uptake of paclitaxel by elacridar a third generation P-gp inhibitor.
- P-gp inhibition can also increase the half-lives of the substrates as the inhibition may reduce billiary excretion and the clearance of the substrates in kidney proximal tubule, increasing renal reuptake.
- Orally co-administered doxorubicin and verapamil have shown to increase peak plasma level, prolong elimination of half-life, and increase volume of distribution of doxorubicin after oral administration.

ii)Antimicrobial therapy[48-53]

- Efflux pumps are now recognized in micro organisms include bacteria , fungi, protozoa.
- P-gp is one of the main ABC transporters that is greatly responsible for MDR in microorganisms.
  Ex:Seral et al examined the influence of inhibitors of P-gp (verapamil, cyclosporine) on the antimicrobial activity of macrolides (erythromycin, clarithromycin, roxithromycin, azithromycin) inhibitors can enhance their accumulations inside the cells and increase antimicrobial actions.

iii)Cancer Chemotherapy[54-57]

- P-gp is overexpressed on the surface of cancer cells and prevents drug accumulation inside the tumor, acting as the efflux pump. It extrudes anticancer drugs before they can reach the intended target. Further, it often mediates the development of resistance of the cells to anticancer drugs. Therefore, the administered drugs remain ineffective or cannot bring the desired output.
- Concurrent administration of cytotoxic drugs and inhibiting agents, like verapamil or cyclosporine, can restrain

P-gp mediated extrusion and facilitate the drug in reaching the targeted area.

CONCLUSION

P-gp is one of the main barriers for delivering drugs properly,P-gp is an important component of BBB and placenta barrier, and functions as a protective biological barrier by extruding toxins, drugs, and xenobiotics out of the cell. It not only causes multidrug resistance in cancer but it has also been found to be responsible for MDR of many other clinically important drugs. Altered P-gp expression can lead to increased susceptibility for development of certain diseases also, such as Parkinson's disease, Alzheimer's disease, and refractory epilepsy. Hence, targeted inhibition of P-gp may represent an important strategy by which this serious clinical problem can be overcome. It is increasingly being recognized to play an important role in processes of absorption, distribution, metabolism, and excretion of many clinically important drugs in humans. Because of its importance in pharmacokinetics, P-gp transport screening has to be incorporated into the drug discovery process. A variety of approaches are being tested to develop P-gp inhibitors or mechanisms to bypass it. Proper inhibition will allow not only an increase in cellular uptake, transport, and half-lives of drugs, but also to predict their pharmacokinetics accurately and targeting at specific region. These advances will result in cost effective therapy and it will shorten the treatment time with optimal drug delivery.

REFERENCES

1. Srivalli KMR and Lakshmi PK. Overview of P-glycoprotein inhibitors: a rational outlook. Braz J Pharm Sci. 2012;48(3):353–67.
2. Sharom FJ. The P-glycoprotein multidrug transporter. Essays Biochem. 2011;50(1):161–78.
3. Edwards JE, Alcorn J, Savolainen J, Anderson BD and McNamara PJ. Role of P-glycoprotein in distribution of nelfinavir across the blood-mammary tissue barrier and blood-brain barrier. Antimicrob Agents Chemother. 2005;49(4):1626–8.
4. Melaine N, Liénard MO, Dorval I, Le Goascogne C, Lejeune H and Jégou B. Multidrug resistance genes and P-glycoprotein in the testis of the rat, mouse, guinea pig, and human. BiolReprod. 2002;67(6):1699–707.
5. Beaulieu E, Demeule M, Ghitescu L and Beliveau R. P-glycoprotein is strongly expressed in the luminal membranes of the endothelium of blood vessels in the brain. Biochem J. 1997;326(Pt 2):539–44.
6. Ma JD, Tsunoda SM, Bertino JS Jr, Trivedi M, Beale KK and Nafziger AN. Evaluation of in vivo P-glycoprotein phenotyping probes: a need for validation. Clin Pharmacokinet. 2010;49(4):223–37.
7. Fortuna A, Alves G and Falcao A. In vitro and in vivo relevance of the P-glycoprotein probe substrates in drug discovery and development: focus on rhodamine 123, digoxin and talinolol. J Bioequiv Availab. 2011:S2.
8. Ruetz S and Gros P. Phosphatidylcholinetranslocase: a physiological role for the mdr2 gene. Cell. 1994;77(7):1071–81.
9. Lin JH and Yamazaki M. Role of P-glycoprotein in parmacokinetics: clinical implications. Clin Pharmacokinet. 2003;42(1):59–98.
10. Varma MVS, Ashokraj Y, Dey CS and Panchagnula R. P-glycoprotein inhibitors and their screening: a perspective from bioavailability enhancement. Pharmacol Res. 2003;48(4):347–59.
11. Sharom FJ, Liu R, Qu Q and Romsicki Y. Exploring the structure and function of the Pglycoprotein multidrug transporter using fluorescence spectroscopic tools. Seminars Cell Dev Biol. 2001;12(3):257–65.
12. Martins A, Vasas A and Schelz Z. Constituents of Carpobrotusedulis inhibit P-glycoprotein of MDR1-transfected mouse lymphoma cells. Anticancer Res. 2010;30(3):829–35.
13. Bansal T, Jaggi M, Khar RK and Talegaonkar S. Emerging significance of flavonoids as P-glycoprotein inhibitors in cancer chemotherapy. J Pharm Pharm Sci. 2009;12(1):46–78.
14. Matsuo H, Wakasugi M and Takanaga H. Possibility of the reversal of multidrug resistance and the avoidance of side effects by liposomes modified with MRK-16, a monoclonal antibody to P-glycoprotein. J Control Release. 2001;77(1–2):77–86.
15. Goren D, Horowitz AT, Tzemach D, Tarshish M, Zalipsky S and Gabizon A. Nuclear delivery of doxorubicin via folate-targeted liposomes with bypass of multidrug-resistance efflux pump. Clin Cancer Res. 2000;6(5):1949–57.

16. Mazel M, Clair P and Rousselle C. Doxorubicin—peptide conjugates overcome multidrug resistance. Anticancer Drugs. 2001;12(2):107-16.
17. Gottesman MN and Pastan I. Biochemistry of multidrug resistance mediated by multidrug transporter. Annu Rev Biochem 1993:62:385-427.
18. Hung LW, Wang I and Nikaido K. Crystal Structure of the ATP-binding subunits of an ABC transporter. Nature. 1998;396:703–7.
19. Booth CL, Pulaski L, Gottesman MM and Pastan I. Analysis of the properties of the N-terminal nucleotide-binding domain of human P-glycoprotein. Biochemistry. 2000;39:5518–26.
20. Tombline G, Bartholomew L, Gimi K, Tyndall GA and Senior AE. Synergy between conserved ABC signature Ser residues in P-glycoprotein catalysis. J BiolChem. 2004;279:5363–73.
21. Yasuhisa K, Michinori M, Kei T, Tohru S and Noriyuki K. ATP hydrolysis dependent multidrug efflux transporter: MDR1/P-glycoprotein. Current Drug Metabolism. 2004;5:1–10.
22. Mark FR, Richard C, Szabolcs M, Christopher FH and Robert CF. Threedimensional Structure of P-glycoprotein The transmembrane regions adopt an asymmetric configuration in the nucleotide -bound state. J BiolChem. 2005;280:2857–62.
23. Shimabuku AM, Nishimoto T, Ueda K and Komano T. P-glycoprotein. ATP hydrolysis by the N-terminal nucleotide-binding domain. J BiolChem. 1992;267:4308–11.
24. Hrycyna CA, Ramachandra M, Ambudkar SV, Ko YH, Pedersen PL and Pastan I. Mechanism of action of human P-glycoprotein ATPase activity. Photochemical cleavage during a catalytic transition state using orthovanadate reveals cross-talk between the two ATP sites. J BiolChem. 1998;273:16631–4.
25. Thiebaut F, Tsumo T, Hamada H, Gottesman MM, Pastan I and Willingham MC. Cellular localisation of the multidrug resistance gene product Pglycoprotein in normal human tissues. Proc Natl Acad Sci. USA, 1987;84:7735-7738.
26. Croop JM, Raymond M, Haber DAD, Arceci RJ, Gros P and Housma DE. The three mouse multidmg resistance (mdr) genes are expressed in a tissue-specific manner in normal mouse tissues. Mol Cell Biol. 1989;9:1346-1350.
27. Arceci RJ, Croop JM, Horwitz S and 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. USA. 1988;85:4350-4354.
28. Joly B, Fardel O, Cecchelli R, Chesn C, Puozzo C and Guillouzo A. Selective drug transport and P glycoprotein activity in an in vitro blood-brain barrier model. Tox In Vitro. 1995;9:357-364.
29. Fardel O, Lecureur V and Guillouzo A. The P-Glycoprotein Multidrug Transporter. Gen Pharmac. 1996;27:1283-1291.
30. Drach D, Zhao S, Drach J and Anoheeff M. Low incidence of MDR1 expression in acute promyelocytic leukaemia. Br J Haematol. 1995;90:369-374.
31. Abolhoda A, Wilson AE, Ross H, Danenberg PV, Burt M and Scotto KW. Rapid activation of MDR1 gene expression in human metastatic sarcoma after in vivo exposure to doxorubicin. Clin Cancer Res. 1999;5:3352–3356.
32. Vishal R Tandon. Plasma glycolprotien-pharmacological relevance, Indian J Pharmacol, February 2006;38(1):13-24.
33. Linn JH and Yamazaki M. Role of P-glycoprotein in pharmacokinetics clinical implications. Clin Pharmacol. 2003;42:59–98.
34. Shapiro AB and Ling V. Effect of quercetin on Hoechst 33342 transport by purified and reconstituted P-glycoprotein. Biochem Pharmacol. 1997;53(4):587–96.
35. Drori S, Eytan GD and Assaraf YG. Potentiation of anticancer drug cytotoxicity by multidrug-resistance chemosensitizers involves alterations in membrane fluidity leading to increased membrane permeability. Eur J Biochem. 1995;228(3):1020–9.
36. Robert J and Jarry C. Multidrug resistance reversal agents. J Med Chem. 2003;46(23):4805–17.
37. Schoenhard GL. Inhibitors of ABC drug transporters at the blood-brain barrier Pain Therapeutics, Inc., US patent No. 2006;7,034,036.
38. Liscovitch M and Lavie Y. Cancer multidrug resistance: A review of recent

drug discovery research. IDrugs. 2002;5:1-7.
39. Thomas H and Coley HM. Overcoming multidrug resistance in cancer: an update on the clinical strategy of inhibiting Pglycoprotein. Cancer Control. 2003;10:159–165.
40. Thomas H and Coley HM. Overcoming multidrug resistance in cancer: an update on the clinical strategy of inhibiting p-glycoprotein. Cancer Control. 2003;10(2):159–65.
41. Krishna R and Mayer LD. Multidrug resistance (MDR) in cancer. Mechanisms, reversal using modulators of MDR and the role of MDR modulators in influencing the pharmacokinetics of anticancer drugs. Eur J Pharm Sci. 2000;11(4):265–83.
42. Newman MJ, Rodarte JC and Benbatoul KD. Discovery and characterization of OC144–093, a novel inhibitor of P-glycoprotein-mediated multidrug resistance. Cancer Res. 2000;60(11):2964–72.
43. Woo JS, Lee CH, Shim CK and Hwang SJ. Enhanced oral bioavailability of paclitaxel by coadministration of the P-glycoprotein inhibitor KR30031. Pharm Res. 2003;20(1):24–30.
44. Banerjee SK, Jagannath C, Hunter RL and Dasgupta A. Bioavailability of tobramycin after oral delivery in FVB mice using CRL-1605 copolymer, an inhibitor of P-glycoprotein. Life Sci. 2000;67(16):2011–16.
45. Eytan GD, Regev R, Oren G and Assaraf YG. The role of passive transbilayer drug movement in multidrug resistance and its modulation. J Biol Chem. 1996;271(22):12897–902.
46. Doppenschmitt S, Spahn-Langguth H, Regardh CG and Langguth P. Role of P-glycoprotein-mediated secretion in absorptive drug permeability: An approach using passive membrane permeability and affinity to P-glycoprotein. J Pharm Sci. 1999;88(10):1067–72.
47. Kwak JO, Lee SH and Lee GS. Selective inhibition of MDR1 (ABCB1) by HM30181 increases oral bioavailability and therapeutic efficacy of paclitaxel. Eur J Pharmacol. 2010;627(1–3):92–8.
48. Gibbons S, Oluwatuyi M and Kaatz GW. A novel inhibitor of multidrug efflux pumps in Staphylococcus aureus. J Antimicrob Chemother. 2003;51(1):13–7.
49. Poole K. Efflux-mediated antimicrobial resistance. J Antimicrob Chemother. 2005;56(1):20–51.
50. Normark BH and Normark S. Evolution and spread of antibiotic resistance. J Intern Med. 2002;252(2):91–106.
51. Poole K. Mechanisms of bacterial biocide and antibiotic resistance. J Appl Microbiol. 2002;92:55S–64.
52. Wright GD. Mechanisms of resistance to antibiotics. Curr Opin Chem Biol. 2003;7(5):563–9.
53. Seral C, Michot JM, Chanteux H, Mingeot-Leclercq MP, Tulkens PM and Van Bambeke F. Influence of P-glycoprotein inhibitors on accumulation of macrolides in J774 murine macrophages. Antimicrob Agents Chemother. 2003;47(3):1047–51.
54. Mazel M, Clair P and Rousselle C. Doxorubicin-peptide conjugates over-come multidrug resistance. Anticancer Drugs. 2001;12(2):107-116.
55. Raub TJ. P-glycoprotein recognition of substrates and circumvention through rational drug design. Mol Pharm. 2005;3(1):3–25.
56. Brigger I, Dubernet C and Couvreur P. Nanoparticles in cancer therapy and diagnosis. Adv Drug Deliv Rev. 2002;54(5):631–51.
57. Soma CE, Dubernet C, Bentolila D, Benita S and Couvreur P. Reversion of multidrug resistance by co-encapsulation of doxorubicin and cyclosporin A in polyalkylcyanoacrylate nanoparticles. Biomaterials. 2000;21(1):1–7.