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*Third-generation P-gp inhibitors can be given with cytotoxic agents with minimal interference with the pharmacokinetics of the cytotoxic agents.*

# Overcoming Multidrug Resistance in Cancer: An Update on the Clinical Strategy of Inhibiting P-Glycoprotein

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**Background:** *Multidrug resistance (MDR) is a significant obstacle to providing effective chemotherapy to many patients. Multifactorial in etiology, classic MDR is associated with the overexpression of P-glycoprotein (P-gp), resulting in increased efflux of chemotherapy from cancer cells. Inhibiting P-gp as a method to reverse MDR in cancer patients has been studied extensively, but the results have generally been disappointing.*

**Methods:** *The development of P-gp inhibitors is reviewed, including a discussion of early agents that are no longer being developed and third-generation agents that are currently in clinical trials.*

**Results:** *First-generation agents (eg, cyclosporin, verapamil) were limited by unacceptable toxicity, whereas second-generation agents (eg, valspodar, biricodar) had better tolerability but were confounded by unpredictable pharmacokinetic interactions and interactions with other transporter proteins. Third-generation inhibitors (tariquidar XR9576, zosuquidar LY335979, laniquidar R101933, and ONT-093) have high potency and specificity for P-gp. Furthermore, pharmacokinetic studies to date have shown no appreciable impact on cytochrome P450 3A4 drug metabolism and no clinically significant drug interactions with common chemotherapy agents.*

**Conclusions:** *Third-generation P-gp inhibitors have shown promise in clinical trials. The continued development of these agents may establish the true therapeutic potential of P-gp-mediated MDR reversal.*

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## Introduction

Multidrug resistance (MDR) in tumor cells is a significant obstacle to the success of chemotherapy in many cancers. Multidrug resistance is a phenomenon whereby tumor cells in vitro that have been exposed to one cytotoxic agent develop cross-resistance to a range of structurally and functionally unrelated compounds. The drug resistance that develops in cancer cells often results from elevated expression of particular proteins, such as cell-membrane transporters, which can result in an increased efflux of the cytotoxic drugs from the cancer cells, thus lowering their intracellular concentrations.<sup>1,2</sup> In addition, MDR occurs intrinsically in some cancers without previous exposure to chemotherapy agents.<sup>3</sup> The cytotoxic drugs that are most frequently associated with MDR are hydrophobic, amphipathic natural products, such as the taxanes (paclitaxel, docetaxel), vinca alkaloids (vinorelbine, vincristine, vinblastine), anthracyclines (doxorubicin, daunorubicin, epirubicin), epipodophyllotoxins (etoposide, teniposide), topotecan, dactinomycin, and mitomycin C.<sup>2,4</sup>

A number of different mechanisms can mediate the development of MDR, including increased drug efflux from the cell by adenosine triphosphate (ATP)-dependent transporters, decreased drug uptake into the cell, activation of detoxifying enzymes, and defective apoptotic pathways.<sup>1</sup> The etiology of MDR may be multifactorial, but the classic resistance to the cytotoxic drugs mentioned above has most often been linked to the overexpression of P-glycoprotein (P-gp), a 170-kd ATP-dependent membrane transporter that acts as a drug efflux pump (Fig 1).<sup>1,5</sup> In addition to cytotoxic drugs, P-gp also transports several other exogenous com-

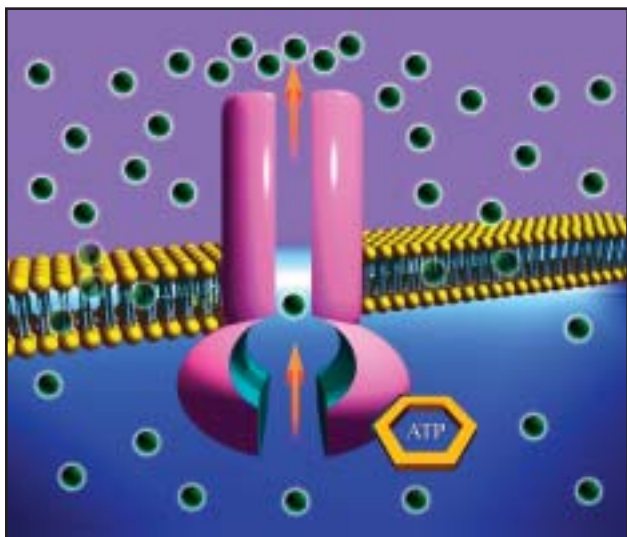


Fig 1. — Mechanism of action of P-glycoprotein (P-gp) inhibitors, showing normal P-gp function in the plasma membrane of a cancer cell during chemotherapy. Activation of the efflux pump by the hydrolysis of a bound ATP molecule drives the cytotoxic drug molecules out of the cell.

pounds, including digoxin, opiates, polycyclic aromatic hydrocarbons, technetium (<sup>99m</sup>Tc) sestamibi, and rhodamine 123. The last two compounds have been used in imaging and in surrogate marker assays of P-gp function in normal and malignant human cells.<sup>6,7</sup> The surrogate marker assay as an indicator of in vivo modulator drug activity relies on examination of the CD56<sup>+</sup> subset of peripheral blood lymphocytes that express functional P-gp. Hence, the changes seen in rhodamine 123 (a substrate for P-gp) uptake by CD56<sup>+</sup> lymphocytes from modulator-treated and untreated whole blood are used as the basis for these types of studies.

P-gp belongs to the ATP-binding cassette (ABC) family of transporters, currently numbering 48 members, that share sequence and structural homology.<sup>8</sup> It is believed that, while this class of transporters has a large number of members, only 10 or so are reported to confer the drug-resistant phenotype.<sup>1</sup> These transporters use the energy that is released when they hydrolyze ATP to drive the transport of various molecules across the cell membrane.<sup>8</sup> In addition to their physiologic expression in normal tissues, many are expressed and, importantly, over-expressed, in human tumors. Their role in the development of MDR and in normal tissues has been reviewed elsewhere.<sup>1</sup> A number of ABC transporters and the chemotherapy drugs to which they have been shown to confer resistance are listed in the Table.

In cancerous tissue, the expression of P-gp is usually highest in tumors that are derived from tissues that normally express P-gp, such as epithelial cells of the colon, kidney, adrenal, pancreas, and liver, resulting in the potential for resistance to some cytotoxic agents before chemotherapy is initiated. In other tumors, the expression of P-gp may be low at the time of diagnosis but increases after exposure to chemotherapy agents, thereby resulting in the development of MDR in those cells.<sup>3</sup> There is a growing body of literature that links the failure of certain chemotherapeutic agents to the expression of P-gp. Indeed, the induction of MDR1 RNA can be rapid following exposure of tumor cells to chemotherapy.<sup>9</sup>

Inhibiting P-gp as a way of reversing MDR has been extensively studied for more than 2 decades. Many agents that modulate the function of P-gp have been identified, including calcium channel blockers, calmodulin antagonists, steroidal agents, protein kinase C inhibitors, immunosuppressive drugs, antibiotics, and surfactants.<sup>10</sup> Perhaps the biggest impetus for pursuing the use of MDR modulators in the clinical setting was provided by the work of Chan et al<sup>11,12</sup> who first showed that the expression of P-gp was a significant prognostic marker in certain childhood malignancies.

This group then used cyclosporin in combination with chemotherapy in retinoblastoma patients and achieved a high cure rate (91% of previously untreated patients remained relapse-free, with salvage therapy combining cyclosporin and chemotherapy prolonging survival in those previously untreated with cyclosporin).<sup>13</sup> Although these trials were limited in size, they raised substantial interest in the cancer research community. However, it is now widely acknowledged that the

major limitation of many of the early agents is that they typically reverse MDR at concentrations that result in unacceptable toxicity.<sup>4,14</sup> This, together with unfavorable pharmacokinetic interactions, prompted the development of a number of new molecules that are more potent and selective for the P-gp transporter. This review compares and contrasts the properties of the new third-generation P-gp inhibitors that are currently in clinical development with those of earlier-generation agents.

P-Glycoprotein and Other ATP-Binding Cassette Transporters Associated With Classic Multidrug Resistance and the Cytotoxic Substrates They Transport

Common Name	Other Names	Systematic Name	Chemotherapy Substrates
P-gp	MDR1	ABCB1	actinomycin-D bisantrone daunorubicin docetaxel doxorubicin etoposide homoharringtonine mitoxantrone <sup>53</sup> paclitaxel teniposide topotecan vinblastine vincristine vinorelbine
MDR2	—	ABCB4	paclitaxel vinblastine
MRP1	—	ABCC1	doxorubicin epirubicin etoposide methotrexate vincristine vinorelbine <sup>54</sup>
CMOAT	MRP2	ABCC2	cisplatin doxorubicin etoposide methotrexate mitoxantrone vincristine
BCRP	MXR, ABC-P	ABCG2	daunorubicin doxorubicin mitoxantrone SN-38 topotecan

P-gp = p-glycoprotein  
MDR = multidrug resistance  
MRP = multidrug resistance protein  
CMOAT = canalicular multi-organic anion transporter  
BCRP = breast cancer resistance protein  
MXR = mitoxantrone resistance  
ABC = ATP-binding cassette

Data from Ambudkar et al,<sup>2</sup> Gottesman et al,<sup>1</sup> Shepard et al,<sup>53</sup> and Dantzig et al.<sup>54</sup>

## P-gp Modulators

Many agents that modulate the P-gp transporter, including verapamil, cyclosporin (cyclosporin A), tamoxifen, and several calmodulin antagonists, were identified in the 1980s.<sup>4</sup> These agents often produced disappointing results in vivo because their low binding affinities necessitated the use of high doses, resulting in unacceptable toxicity.<sup>4,10</sup> Many of the first chemosensitizers identified were themselves substrates for P-gp and thus worked by competing with the cytotoxic compounds for efflux by the P-gp pump; therefore, high serum concentrations of the chemosensitizers were necessary to produce adequate intracellular concentrations of the cytotoxic drug.<sup>2</sup> In addition, many of these chemosensitizers are substrates for other transporters and enzyme systems, resulting in unpredictable pharmacokinetic interactions in the presence of chemotherapy agents. To overcome these limitations, several novel analogs of these early chemosensitizers were tested and developed, with the aim of finding P-gp modulators with less toxicity and greater potency.<sup>4</sup>

### Second-Generation P-gp Modulators

The second-generation P-gp modulators include dexverapamil, dexniguldipine, valspodar (PSC 833), and biricodar (VX-710). These agents are more potent than their predecessors and also less toxic.<sup>4</sup> The best characterized and most studied of these agents is valspodar, a nonimmunosuppressive derivative of cyclosporin D that inhibits P-gp with 10- to 20-fold greater activity than cyclosporin A.<sup>15,16</sup> Valspodar has been studied in numerous clinical trials in combination with cytotoxic agents.<sup>17-26</sup> A study by Coley et al<sup>27</sup> that used fresh tumor material from patients with soft-tissue sarcomas indicated that valspodar at 1 nM had a modest effect (20% increase) on anthracycline accumulation in P-gp-positive samples. Moreover, in another study looking at MDR in epithelial ovarian cancer, the effect was of a similar magnitude in similar experiments<sup>28</sup> and may go some way toward explaining the disappointing results in clinical trials.

The pipercolinate derivative biricodar citrate (VX-710) has also undergone extensive clinical development. This molecule interferes with drug efflux by directly binding with high affinity to the P-gp pump<sup>29,30</sup> and also by inhibiting the ABC transporter MRP1.<sup>31</sup> The coadministration of second-generation P-gp modulators and chemotherapy agents in clinical trials has resulted in the reversal of MDR and some limited success in treating refractory cancers.<sup>20,32</sup>

### *Limitations of Second-Generation P-gp Modulators*

Second-generation P-gp modulators have a better pharmacologic profile than the first-generation compounds, but they also retain some characteristics that limit their clinical usefulness. In particular, these compounds significantly inhibit the metabolism and excretion of cytotoxic agents, thus leading to unacceptable toxicity that has necessitated chemotherapy dose reductions in clinical trials.

In response to cytotoxic agents, cytochrome P450 enzymes are often induced along with members of the ABC transporter family, and it is thought that the genes of these families share overlapping regulatory elements.<sup>33</sup> In fact, many of the cytotoxic agents that are substrates for P-gp are also substrates for the cytochrome P450 isoenzyme 3A4. It is not surprising then that the agents that are affected by the development of MDR are also metabolized by cytochrome P450 3A4. Several of the second-generation P-gp modulators, including valsopodar and biricodar, are substrates for this enzyme.

The competition between cytotoxic agents and these P-gp modulators for cytochrome P450 3A4 activity has resulted in unpredictable pharmacokinetic interactions. For example, valsopodar inhibits the cytochrome P450 3A4-mediated metabolism of paclitaxel and vinblastine,<sup>34</sup> resulting in increased serum concentrations of the cytotoxic agents and potentially putting patients at risk of cytotoxic drug overexposure.<sup>23,35</sup> Similarly, in a pharmacokinetic study in patients with solid tumors, biricodar administered in a 24-hour intravenous infusion decreased the clearance of paclitaxel in a dose-dependent manner.<sup>36</sup> It has been suggested that this interaction may be due in part to the inhibition of cytochrome P450 3A4 by biricodar, thereby interfering with the metabolism of paclitaxel.

The most common response of clinical researchers to this drug interaction has been to reduce the dose of the cytotoxic agent. However, it should be noted that since the pharmacokinetic interactions between chemosensitizers and cytotoxic agents are unpre-

dictable and cannot be determined in advance, reducing the dose of a cytotoxic agent by a set percentage may result in under- or over-dosing in a significant number of patients.<sup>1,35</sup> The unpredictability of the effects of second-generation P-gp modulators on cytochrome P450 3A4-mediated drug metabolism has made it difficult to establish a safe but effective dose of the coadministered chemotherapy agent and thus limits the use of these second-generation modulators in the treatment of multidrug-resistant cancers.

In addition to inhibiting P-gp, many second-generation modulators also function as substrates for other transporters, particularly those of the ABC transporter family, inhibition of which could lessen the ability of normal cells and tissues to protect themselves from cytotoxic agents. Many of these transporters have well-defined physiologic roles, often involving the elimination of xenobiotics (in the case of those transporters in the liver, kidney, and gastrointestinal tract).<sup>4</sup> In addition, ABC transporters are involved in regulating the permeability of the central nervous system (blood-brain barrier), the testes, and the placenta, thus preventing these systems from being exposed to cytotoxic agents circulating in the blood.<sup>33</sup>

Many of the early-generation P-gp modulators inhibited several other ABC transporters as well as the P-gp transporter. For instance, valsopodar and biricodar are not specific solely to P-gp; both of these agents affect MRP1.<sup>4,31,36</sup> It is possible that this inhibition of non-target transporters may lead to greater adverse effects of anticancer drugs, including neutropenia and other myelotoxic effects. For example, the ABC transporter BCRP is a functional regulator of hematopoietic stem cells<sup>37</sup> and its inhibition may contribute to these effects.

### *Third-Generation P-gp Inhibitors*

Third-generation molecules that specifically and potentially inhibit P-gp function have been developed by using structure-activity relationships and combinatorial chemistry to overcome the limitations of the second-generation P-gp modulators.<sup>4</sup> These agents do not affect cytochrome P450 3A4 at relevant concentrations,<sup>34,38</sup> thus explaining, at least in part, why they do not alter the plasma pharmacokinetics of paclitaxel in rats.<sup>39,40</sup> Similarly, third-generation agents typically do not inhibit other ABC transporters (albeit they have not been tested against all of the ABC transporters). This specificity for the P-gp pump minimizes the possibility that the blockade of more than one pump might result in altered bioavailability or excretion of the chemotherapy agents. These preclinical data have translated to clinical trials, in which none of the third-generation agents have caused clinically relevant alterations in the

pharmacokinetics of the coadministered cytotoxic agents (see below). Consequently, chemotherapy dose reductions have been unnecessary.

The third generation P-gp inhibitors currently in clinical development include the anthranilamide derivative tariquidar (XR9576),<sup>41</sup> the cyclopropyldibenzosuberane zosuquidar (LY335979),<sup>38,42</sup> laniquidar (R101933),<sup>43</sup> and the substituted diarylimidazole ONT-093.<sup>44</sup> Despite having diverse chemical structures and origins, these agents have in common a high potency and specificity for the P-gp transporter. The modulator elacridar (GF120918/GG918), while not as P-gp-specific as agents such as tariquidar, has been shown to inhibit breast cancer resistance protein BCRP.<sup>45</sup>

One of the most promising third-generation P-gp inhibitors is tariquidar, which binds with high affinity to the P-gp transporter and potently inhibits its activity.<sup>41,46</sup> Second-generation P-gp modulators compete as a substrate with the cytotoxic agent for transport by the pump (Fig 2). In contrast, tariquidar specifically and noncompetitively binds to the pump (Fig 3) with an affinity that greatly exceeds that of the transported substrates.<sup>43</sup> It is not clear whether the binding of XR9576 on P-gp is indeed to that of the ATP binding site, but like other modulators such as GF120918, it inhibits the ATPase activity of P-gp.<sup>46</sup>

The inhibitory effects of tariquidar on the P-gp transporter pump greatly exceed those of first- and second-generation P-gp modulators with respect to potency and duration of action. In an *in vitro* study, P-gp pump transport remained blocked for more than 22 hours after tariquidar had been removed from the cul-

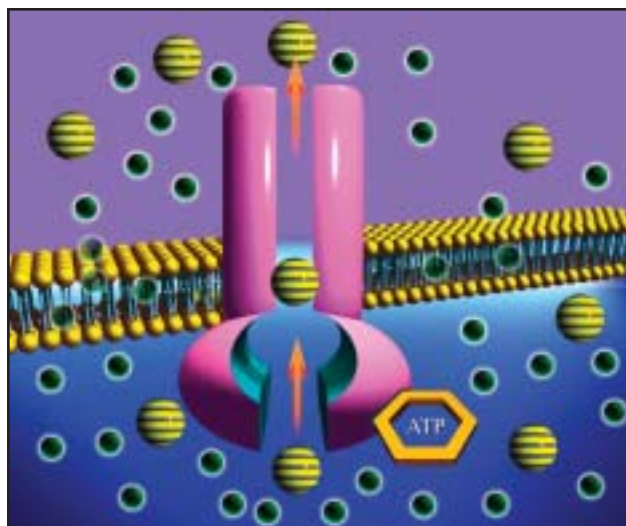


Fig 2. — Competitive inhibition of the P-glycoprotein transporter. First- and second-generation modulators compete as a substrate with the cytotoxic agent for transport by the pump. This limits the efflux of the cytotoxic agent, increasing its intracellular concentration.

ture medium; in the same assay, the clearance time for cyclosporin was 60 minutes.<sup>39</sup> Pharmacokinetic studies in healthy subjects show that single doses of tariquidar up to 2 mg/kg intravenously or 750 mg orally are well tolerated and provide complete P-gp inhibition for at least 24 hours, as shown by rhodamine 123 accumulation in CD56<sup>+</sup> lymphocytes.<sup>47</sup> A single intravenous dose of tariquidar in patients with cancer inhibited the efflux of rhodamine from CD56<sup>+</sup> cells for up to 48 hours.<sup>48</sup> Tariquidar showed no effect on the pharmacokinetics of paclitaxel, vinorelbine, or doxorubicin when it was administered to patients with solid tumors.<sup>48-50</sup> This allowed the use of standard doses of these chemotherapeutic agents without the need for dose reduction. Tariquidar is currently in phase III trials in patients with non-small-cell lung cancer.

The cyclopropyldibenzosuberane modulator LY335979 was shown to competitively inhibit the binding of vinblastine to P-gp.<sup>40</sup> In clinical studies in both solid and hematologic malignancies, LY335979 showed no significant pharmacokinetic interactions with doxorubicin, etoposide, daunorubicin, vincristine, or paclitaxel.<sup>38,42,51,52</sup> R101933 and ONT-093 are two other third-generation P-gp inhibitors that have been shown to be effective in inhibiting P-gp with no effect on the pharmacokinetics of docetaxel<sup>43</sup> and paclitaxel.<sup>44</sup>

## Conclusions

Because of their specificity for P-gp transporters and lack of interaction with cytochrome P450 3A4, third-generation P-gp inhibitors offer significant

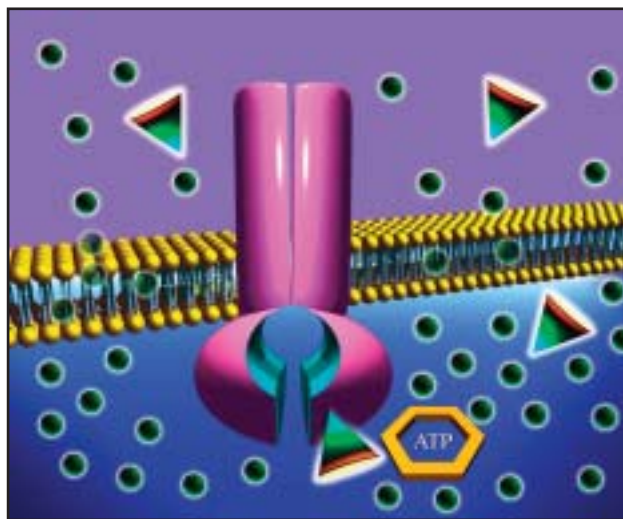


Fig 3. — Noncompetitive inhibition of the P-glycoprotein transporter. Third-generation inhibitors of P-gp, such as tariquidar, bind with high affinity to the pump but are not themselves substrates. This induces a conformational change in the protein, thereby preventing ATP hydrolysis and transport of the cytotoxic agent out of the cell, resulting in an increased intracellular concentration.

advantages over the second-generation agents. The results of clinical trials to date show that third-generation P-gp inhibitors such as tariquidar, LY335979, R101933, and ONT-093 can be given with full therapeutic doses of cytotoxic agents and with minimal interference with the pharmacokinetics of the cytotoxic agents. Ongoing clinical trials with these new agents should show whether this approach will result in greater survival in patients with cancer. Thus far, this objective has not been demonstrated, due in part to the unpredictable pharmacokinetic effects of second-generation P-gp modulators on the coadministered chemotherapy agents. The preliminary results with third-generation P-gp inhibitors offer new hope that this goal might be realized.

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