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Letter to the Editor

# Decreasing Drug Resistance Through Modulation/ Inhibition of the P-Glycoprotein

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Drug resistance occurs through multiple mechanisms within a tumor cell. A well-documented mechanism of drug resistance has been identified through the expression of the P-glycoprotein (Pgp), also known as the multidrug resistance 1 (MDR1) protein [1,2]. This overexpression of the Pgp in tumor cells is responsible for the resistance of certain chemotherapy agents that are used for treating late stage cancer patients [3].

The Pgp is encoded by the ABCB1 gene, which is located on 7q21.12 with 29 exons [2,4]. The Pgp is a transmembrane protein with 1280 amino acids consisting of 12 transmembrane domains and 2 cytoplasmic domains with an ATP-binding site. This transporter is a member of the superfamily of ATP-binding cassette (ABC) transporters which is divided into seven distinct subfamilies [5]. The Pgp is expressed in the liver, the adrenal gland, intestines, kidneys, placenta, and the capillary endothelial cells of the brain and testis barriers [6]. The function of this protein is to transport substrates across the membrane of the cell using the active transport through ATP activation. In cases such as the blood-brain barrier and the intestines, the Pgp plays a protective role by using the efflux pump to excrete toxins and xenobiotic compounds from the cell before the harmful substrates are able to damage the tissues or organism [6].

In drug metabolism, the Pgp is able to transport drug substrates in or out of the cell, depending on the composition of the compound. There is a wide variety of substrates of the Pgp, these drugs include immunosuppressants, calcium blockers, beta-blockers, antihistamines, anticonvulsants, antidepressants, chemotherapy agents, and retroviral inhibitors [7]. The CYP3A4 is the CYP450 enzyme that is complimentary to the Pgp for metabolizing many of the drug therapies. The Pgp is able to transport the drug into the cell where the drug then becomes a substrate for CYP3A4 [8,9].

The Pgp has been well characterized by researchers because of the increase of the Pgp efflux with chemotherapy agents in tumor cells. The increase of the Pgp efflux leads to the tumor cells becoming resistant to the chemotherapy agents. The Pgp substrates of chemotherapy agents include taxanes (paclitaxel, docetaxel), vinca alkaloids (vincristine, vinblastine), anthracyclines (doxorubicin, daunorubicin), and epipodophyllotoxins (etoposide) [1]. These agents are cytotoxic to tumor cells and are used to treat patients with lymphoma, leukemia, lung cancer, breast cancer, colorectal cancer, or other types of solid tumors.

In tumor cells, the increase of efflux in the Pgp occurs through over expression of the protein which can happen through somatic or epigenetic alterations in the tumor cells. These genetic changes can occur before or after the initiation of chemotherapy. One type of alteration associated with increased Pgp expression is the somatic mutations of either oncogenes, such as Ras and raf kinase, or the tumor suppressor gene, TP53. Somatic mutations in these cancer driver genes have been implicated with regulating the expression of the ABCB1 gene [10-12]. Another reason for increased Pgp expression in tumor cells is through the epigenetic changes of demethylation in the promoter of the ABCB1 gene or histone deacetylation. Several in vitro studies with leukemia, breast cancer, and bladder cancer have demonstrated that the loss of methylation in the ABCB1 promoter is associated with the activation of Pgp expression in drug resistant cells [13-15]. The acetylation status of histones was also associated with the increased expression of Pgp in colorectal and sarcoma cells through *in vitro* experiments. Researchers identified that the increased acetylation of histone H3 influenced the expression of several ABC transporters such as Pgp [16,17]. Identifying these somatic or epigenetic changes in the multi-drug resistant tumor cells may play an important role in the future for the use of targeted therapy for regulating the Pgp expression.

Several approaches have been developed to reverse the effects of drug resistance in the tumor cells. This reversal of drug resistance can be achieved through competition or inhibiting efflux pump of the Pgp. Decreasing the Pgp activity can be accomplished through the use of either modulators or inhibitors for the Pgp. These modulators and inhibitors for Pgp are drugs that are currently being used for treatment. Thirty years ago, researchers identified the first generation of Pgp modulators [18]. These drugs are able to compete with the chemotherapy agents for the Pgp efflux pump. The drugs included the immunosuppressant, cyclosporin A, and calcium channel blocker, verapamil [19,20]. Through *in vitro* and *in vivo* studies, the modulators were unsuccessful for decreasing drug resistance due to toxicity issues and unpredictable drug interactions [21,22]. A second generation Pgp modulators were identified to increase potency of binding to the efflux pump and decreasing the issues of toxicity from the lesson learned in the first generation modulators. One of the most studied second generation modulators was the Valspodar (PSC833), which is a derivative of cyclosporine D [18,23]. Using *in vitro* studies, the experimental Valspodar in conjunction with chemotherapy agents resulted with a higher effect of binding to the efflux pump than the first generation Pgp modulators, but the second generation modulator and chemotherapy agents were discovered to be both substrates for CYP3A4 [24,25]. This discovery showed that the competition for the CYP3A4 caused a decrease in the metabolism of the chemotherapy agents. This competition for CYP3A4 led to less of the active chemotherapy agent to kill the tumor cells [26]. The third generation of Pgp modulators/inhibitors such as




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Tariquidar, Zosuquidar, Sorafenib, and Lapatinib are being studied as potential drugs for lowering the efflux activity of the Pgp and may be successful for decreasing drug resistance [27-31]. Some of these third generation drugs are currently being used in clinical trials as an option for decreasing drug resistance in several cancers including lung, colorectal, and breast.

In future oncology treatment, personalized therapy will be available for cancer patients. A wide variety of chemotherapy agents and targeted cancer therapies will be able to remove the issues of multi-drug resistance in tumor cells. With the identification of increase Pgp in primary tumors, patients will be placed on drugs that are able to either suppress the Pgp or the patient will be given another drug that is not a Pgp substrate. The increase of cancer therapy options will lead to better outcomes for late cancer patients.

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