

## Pharmacogenomic Analysis Identifies Increased Efficacy of Oxaliplatin in *ABCB1* Overexpressing Tumors

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### Abstract

Oxaliplatin is a platinum-class drug used for advanced colorectal cancer, which is still incurable because of drug resistance. We applied a pharmacogenomic approach to correlate mRNA expression profiles of transporter genes and growth inhibitory potency of oxaliplatin in NCI-60. Expression of *ABCB1* (MDR1, P-glycoprotein) gene positively correlated with anticancer activity of oxaliplatin, but not with cisplatin and other platinum analogs. This correlation suggests that cell lines with higher *ABCB1* expression were more sensitive to oxaliplatin. MDR1 inhibitors cyclosporine A, PSC 833 or verapamil significantly reduced the sensitivity to oxaliplatin in *ABCB1* overexpressing ovarian cancer cell line NCI/ADR-RES and colon cancer cell line HCT-15, whereas increased the sensitivity to MDR1 substrate drugs. These results provide evidence that the effect of oxaliplatin may be selective for tumor cells with high level of *ABCB1* and overcome drug resistance. Such finding may provide an exciting prospect for future individualization of oxaliplatin-based cancer therapy.

**Keywords:** Pharmacogenomics; Chemotherapy; Colon cancer; oxaliplatin; P-glycoprotein

### Introduction

Colorectal Cancer (CRC) is ranked the third most common cancers in both female and male in the US in 2010 [1]. There are 142,570 estimated new cases and 51,370 deaths from colon cancer in the United States in 2010 [1,2]. The primary treatment for CRC is surgery but the risk of recurrence due to undetected micro metastases is high. To reduce this risk, chemotherapy is normally used after removal of the primary tumors in the advanced stage. Currently, there are seven approved chemotherapeutic drugs for patients with metastatic CRC: 5-fluorouracil (5-FU), capecitabine, irinotecan, oxaliplatin, bevacizumab, cetuximab, and panitumumab (National Cancer Institute website:

<http://www.cancer.gov/cancertopics/pdq/treatment/colon/HealthProfessional/page9>).

For advanced CRC, 5-FU therapy in combination with leucovorin (known as FL) produces response rates of only 20-25% [3]. Efforts to improve efficacy has led to a new combination regimen of 5-FU/leucovorin plus oxaliplatin (known as FOLFOX), which has significantly improved response rate to 40-50% [4]. Therefore, oxaliplatin-based combination chemotherapy is now routinely used for late stage CRC.

Oxaliplatin (trans-1,1,2-diaminocyclohexane oxalatoplatinum) is the third generation platinum derivative with a 1,2-diaminocyclohexane (DACH) carrier ligand [5]. Although the precise mechanism of action is unknown, platinum compounds are thought to exert their cytotoxic effects through the formation of DNA adducts that block both DNA replication and transcription, resulting in cell death in actively dividing cells. Like the first generation platinum derivative cisplatin, oxaliplatin reacts with DNA, forming mainly platinated intra-strand links with two adjacent guanines or a guanine adjacent to an adenine [6-8]. The DACH-platinum adducts formed by oxaliplatin are apparently more effective at inhibiting DNA synthesis [8] and are more cytotoxic than the cis-diamine-platinum adducts formed from cisplatin and carboplatin [8]. Although cisplatin, carboplatin, and oxaliplatin have similar DNA-

binding properties, only oxaliplatin is the chemotherapeutic agent that is active in the treatment of Stage II, Stage III, and Stage IV CRC [9]. The mechanism of this tumor-specific activity are not clear but may be related to the difference in transporter-mediated drug uptake or efflux [10].

Although the addition of oxaliplatin can provide enhanced treatment outcome in patients with CRC, about 50% of CRC patients are not responsive because of drug resistance. Drug resistance is one of the main causes of failure in the treatment of cancer [11], which may lead to disease recurrence or death. The efficacy of oxaliplatin for individual patient is largely unpredictable such that at the start of chemotherapy it is unclear whether an individual patient will benefit from the treatment or not. Inappropriate chemotherapy can actually result in the selection of more resistant and aggressive tumor cells [11]. Such difficulties highlight the need to identify and develop predictive biomarkers for selecting right drugs for the right patients. One exciting potential to tackle the problem is the use of molecular biomarkers to identify individuals who may or may not benefit from certain cancer therapy.

There are two general types of resistance to anticancer drugs: those that involve delivery of anticancer drugs to tumor cells, and those that occur in the cancer cell itself due to genetic or epigenetic alterations [12]. Regardless of which type of resistance, cancer cells can become resistant to a single drug or to a family of drugs with similar

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mechanism of action. They may also acquire broad cross-resistance to mechanistically and structurally unrelated drugs, a phenomenon known as Multi Drug Resistance (MDR). Multiple mechanisms may contribute to MDR, including reduced drug uptake, increased drug efflux, abnormal metabolism and inactivation by glutathione or other self-defense molecules [11]. The mechanisms controlling the cellular uptake and efflux of oxaliplatin and other platinum compounds, albeit rarely investigated, may be important because reduced intracellular accumulation is the most common observation in cisplatin-resistant cells [13].

Recent studies indicate that membrane transporters play an important role in drug disposition and metabolism in the human body and tumor cells, thereby potentially affecting the efficacy of drug therapy [14]. Transporters are particularly important in the chemotherapy of cancer because the effectiveness and side effects of chemotherapy often depends on the relative transporter activities in normal and cancer cells. A recent study by Zhang et al. [10] showed that the human organic cation transporters OCT1 and 2 (SLC22A1 and SLC22A2), but not OCT3 (SLC22A3), markedly increase oxaliplatin, but not cisplatin, accumulation and cytotoxicity in transfected cells, indicating that oxaliplatin is an excellent substrate of these transporters. However, Yonezawa et al. [15] reported that oxaliplatin, but not cisplatin, was transported by human and rat organic cation transporter 3 (OCT3). In addition, the copper influx transporter Ctr1 (SLC31A1) has been found to be involved in cellular uptake of cisplatin and oxaliplatin, but may not affect the formation and cytotoxicity of platinum-DNA adducts [16,17]. Furthermore, the copper efflux transporters ATP7B and ATP7A were also reported to affect intracellular accumulation of platinum compounds [13]. Despite the current progress in transporter research, the importance of these transporters in modulating the differential activity and tumor specificity of oxaliplatin as well as the clinical implication are currently unknown. Given the large number of transporters (~4% of genes in the human genome [18]) as well as the effects from coordinated activity of various efflux and uptake transporters, only a very small percentage of the possible pharmacological interactions have been studied. A systematic investigation of the transporters' role in sensitivity and resistance to oxaliplatin is lacking.

We have developed a pharmacogenomic approach to study the potential pharmacological interactions between transporter proteins and anticancer drugs [18]. We applied a custom designed DNA microarray to analyze gene expression of a majority of human membrane transporters in the NCI-60 cell panel, which is used by the Developmental Therapeutics Program (DTP) of the National Cancer Institute (NCI) for anticancer drug screening. Included among the NCI-60 are leukemias, melanomas, and cancers of ovarian, breast, prostate, lung, renal, colon, and central nervous system origin. The NCI-60 panel is an ideal and practical system for pharmacogenomic studies, because over 100,000 chemical compounds and natural products extracts have been screened using the NCI-60 cell panel for in vitro anticancer activities since 1990. Correlating gene expression levels with the growth inhibitory potencies of anticancer drugs in the NCI-60 cells, we have identified many known drug-transporter interactions and identified novel ones [18-22].

In the present study, this approach was utilized to identify novel transporters related to oxaliplatin sensitivity. Interestingly, the gene encoding the P-glycoprotein (P-gp), ABCB1, was found to positively correlated with the activity of oxaliplatin against NCI-60. Thus, a

follow up functional assay was carried out to validate the novel ABCB1-oxaliplatin interaction.

## Materials and Methods

### Compound potency databases of NCI-60

The September 2008 release of the National Cancer Institute (NCI) antitumor drug screening database was obtained from the NCI's DTP website (Human Tumor Cell Line Screen: [http://dtp.nci.nih.gov/docs/cancer/cancer\\_data.html](http://dtp.nci.nih.gov/docs/cancer/cancer_data.html)), containing non-confidential screening results and chemical structural data from the DTP. For each compound and cell line, growth inhibition after 48 h of drug treatment had been assessed from changes in total cellular protein using a sulforhodamine B (SRB) assay [23]. The data provide GI<sub>50</sub> values for each compound-cell line pair (GI<sub>50</sub>, the concentration causing 50% growth inhibition).

### Gene expression databases of NCI-60

A customized oligonucleotide microarray containing probes targeting 461 transporter and 151 channel genes, as well as 100 probes for unrelated genes was used to measure transporter gene expression in NCI-60. Array hybridization, data analysis and database were described in previous study [18]. A second gene expression database generated by Affymetrix U133 was also employed for gene-drug correlation analysis (available at NCI's Developmental Therapeutics Program (DTP) website (<http://dtp.nci.nih.gov/mtargets/download.html>)).

### Correlation of gene expression profiles with compound potency patterns

Pearson correlation coefficients were calculated to correlate gene expression profiles with patterns of oxaliplatin activities across the NCI-60:

$$r_{A_i T_j} = \frac{s_{A_i T_j}}{s_{A_i} s_{T_j}}$$

where  $s_{A_i}$  is activity standard deviation of  $i^{\text{th}}$  compound,  $s_{T_j}$  is expression standard deviation of  $j^{\text{th}}$  gene, and  $s_{A_i T_j}$  is covariance. P values for the correlation coefficients were obtained by fitting a linear regression model.

### Chemicals

Oxaliplatin was obtained from Sanofi-Aventis (Paris, France). Other chemicals were purchased from Sigma Chemical Co. (St. Louis, Missouri, USA).

### Cell culture

All the cell lines were obtained from Division of Cancer Treatment and Diagnosis at NCI and cultured in RPMI 1640 medium containing 5 mM L-glutamine, supplemented with 10% FBS, 100 U/ml penicillin G and 100 µg/ml streptomycin. Cells were grown in tissue culture flasks at 37°C in a 5% CO<sub>2</sub> atmosphere.

### Cell proliferation assay

Growth inhibitory potency was tested using a proliferation assay with sulforhodamine B (SRB), a protein-binding reagent (Sigma), as described before [18] or MTS assay (Promega). 3000-4000 cells/well were seeded in 96-well plates and incubated for 24 h. Before exposure to test compounds, cells were treated individually with CsA, PSC833 or verapamil or medium (as control) for 10 min. Test compounds were added in a dilution series in three replicated wells for 3 days. To determine IC<sub>50</sub> values, the absorbance of control cells without drug

was set at 1. Dose-response curves were plotted using Prism software (San Diego, California, USA). Each experiment was performed independently at least twice. Student's t test was used to determine the degree of significance.

## Results

### Pharmacogenomic analysis based on the NCI-60 cell panel

In light of the importance of drug transporters, we designed and produced a DNA microarray detecting mRNA expression of genes encoding the majority of proteins involved in membrane transport, including transporters and channels [18]. We then applied these arrays to a study of the NCI-60 cell panel and correlated the resulting expression patterns with potency data for various sets of anticancer agents. These studies established a large number of significant drug-transporter relationships [14,18,19,22-26]. Based on these relationships, we identify which transporters would be more likely than others to play a role in oxaliplatin sensitivity and resistance.

Pearson correlation analysis was conducted to systematically integrate the gene expression data from microarrays and the drug activity data obtained from NCI database for oxaliplatin (NSC 266046) (available from the NCI DTP website <http://dtp.nci.nih.gov/>). By ranking the correlation coefficients, and also considering known function of drug transporters, we selected a number of candidate genes that would be potential determinants for oxaliplatin sensitivity or resistance. The transporter genes correlated with oxaliplatin potencies are the organic cation transporter SLC22A2 (OCT2) ( $r=0.33$ ,  $P<0.05$ ), the reduced folate carrier SLC19A1 (RFC1) ( $r=0.38$ ,  $P<0.05$ ), the membrane efflux transporter ABCB1 (MDR1, P-gp) ( $r=0.26$ ,  $P<0.05$ ), and the cystine/glutamate transporter SLC7A11 (xCT) ( $r=-0.21$ ,  $P<0.05$ ).

Since the relationship established between compound activity and transporter genes is merely correlative, such relationship needs to be experimentally validated. The present study focuses on the role of ABCB1 serving as the chemo sensitizing factor for oxaliplatin. Since P-gp extrudes molecules from the cell, the activity patterns of its substrates across the NCI-60 are expected to be negatively correlated with its pattern of expression [18,22,24]. Unexpectedly, oxaliplatin showed a positive correlation with ABCB1 expression, suggesting that

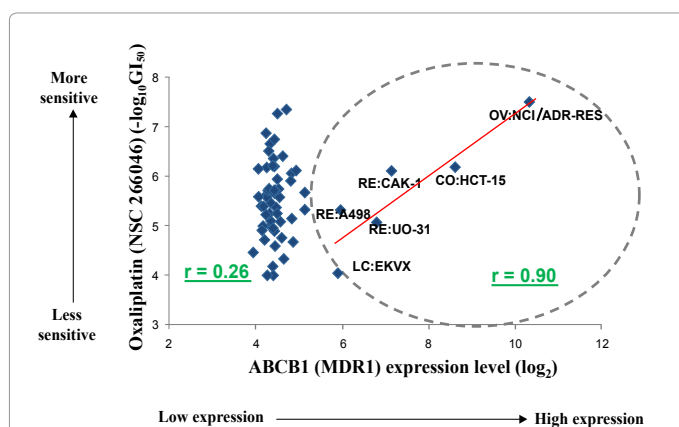
it is not a substrate for P-gp, and moreover, its cytotoxicity may be potentiated, rather than antagonized, by P-gp. A similar phenomenon has been reported previously by Dr. M. Gottesman's group for a compound with unknown mechanism of action, NSC73306 [27]. To verify this interesting but unexpected finding, the mechanism for P-gp-mediated hypersensitivity needs to be further studied.

ABCB1 (P-gp) expression showed a modest but significant correlation with oxaliplatin in the systematic screening including all the 60 cell lines ( $r=0.26$ ,  $P<0.05$ ) (Figure 1). The positive correlation suggests that the cell lines with higher P-gp expression have higher sensitivity to oxaliplatin. When only including the cells with high P-gp expression, i.e., log2 transformed expression value  $>6$  (circled area in Figure 1), to calculate the correlation, significantly stronger correlation was obtained ( $r=0.90$ ,  $P<0.05$ ). This correlation was not observed for other platinum analogs including cisplatin, carboplatin and tetraplatin (data not shown).

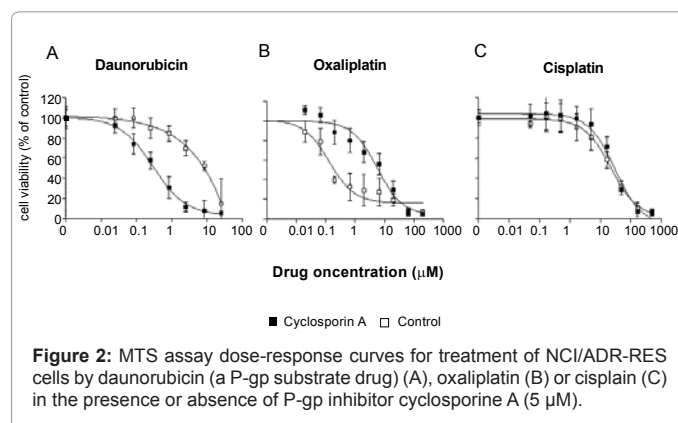
To validate the oxaliplatin-ABCB1 correlations, we calculated the difference in cytotoxic potency (GI50 values, data obtained from <http://dtp.nci.nih.gov/>) between cell lines NCI/ADR-RES (high P-gp) and OVCAR-8 cells (low P-gp). NCI/ADR-RES and OVCAR-8 cells express different amount of P-gp, otherwise the two cell lines are similar in overall gene expression pattern [28]. Oxaliplatin is approximately 190 times more potent against NCI/ADR-RES cells than OVCAR-8 cells. In contrast, all the P-gp substrate drugs such as doxorubicin, paclitaxel and geldanamycins were less potent against NCI/ADR-RES than OVCAR-8 [18,24].

### Functional assay to validate the pharmacogenomic results

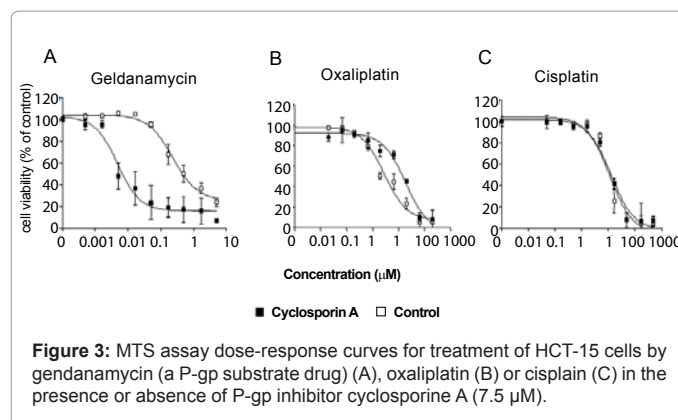
The positive correlation between oxaliplatin activity and ABCB1



**Figure 1:** Scatter plot showing positive correlation ( $r=0.26$ ,  $P<0.05$ ) of ABCB1 expression with sensitivity of the 60 cell lines to oxaliplatin (NSC266046). When only the cells with high P-gp expression, i.e., log2 transformed value  $>6$ , (circled area in Figure 1) were included to calculate the correlation, significantly stronger correlation was obtained ( $r=0.90$ ,  $P<0.05$ ). This correlation was not observed for cisplatin and other platinum analogs.



**Figure 2:** MTS assay dose-response curves for treatment of NCI/ADR-RES cells by daunorubicin (a P-gp substrate drug) (A), oxaliplatin (B) or cisplatin (C) in the presence or absence of P-gp inhibitor cyclosporine A (5  $\mu$ M).



**Figure 3:** MTS assay dose-response curves for treatment of HCT-15 cells by geldanamycin (a P-gp substrate drug) (A), oxaliplatin (B) or cisplatin (C) in the presence or absence of P-gp inhibitor cyclosporine A (7.5  $\mu$ M).

expression suggests that oxaliplatin can inhibit growth of cancer cells more strongly if P-gp is overexpressed. Since such results may come from false positive prediction, we used the MTS cell proliferation assay in the cell lines with high levels of P-gp expression or in the presence or absence of P-gp inhibitors to test our hypothesis. We firstly examined the effect of the P-gp inhibitor cyclosporine A (CsA) on the P-gp over-expressing cell line NCI/ADR-RES.

As expected, for the well-known P-gp substrate drug daunorubicin, treatment with 5  $\mu$ M CsA, the commonly used concentration for P-gp inhibition, significantly increased its chemosensitivity (Figure 2A). However, treatment with 5  $\mu$ M CsA significantly reduced the chemosensitivity of oxaliplatin (Figure 2B). No effect for CsA was observed on potency of cisplatin, an analog of oxaliplatin (Figure 2C).

Similar results were obtained with a P-gp overexpressing colon cancer cell line HCT-15 (Figure 3). HCT-15 is another cell line in the NCI-60 panel with high level of P-gp expression (Figure 1). As expected, for the P-gp substrate drug geldanamycin, treatment with 5.0 and 7.5  $\mu$ M CsA increased its chemosensitivity, while only 7.5  $\mu$ M CsA had significant effect (Figure 3A). However, treatment with 7.5  $\mu$ M CsA significantly reduced the chemosensitivity of oxaliplatin (Figure 3B). No effect for CsA was observed on potency of cisplatin (Figure 3C).

Similar results were obtained with other P-gp inhibitors such as PSC 833 (5  $\mu$ M) or verapamil (10  $\mu$ M) (data not shown).

## Discussion

Of the hundreds of membrane transporters, the multidrug resistance transporter ABCB1 [MDR1/P-glycoprotein (P-gp)] is the best known and most important mediator of MDR [26]. It mediates resistance to multiple classes of compounds with diverse chemical structures and mechanisms of action. The substrates for P-gp are commonly hydrophobic drugs with a polyaromatic backbone, having neutral or positive charge. Examples include anthracyclines, Vinca alkaloids, taxanes and epipodophyllotoxins [29]. In tumor cell lines, ectopic P-gp expression reduces the intracellular accumulation of its substrate drugs. On the other hand, administration of P-gp inhibitors (or modulators) increases their accumulation as well as chemosensitivity [26]. P-gp is highly expressed in some tumors, including kidney, liver and colon cancer [30]. The expression of P-gp has also been correlated with poor prognosis [31]. The recurrent tumors often acquire MDR, either by adaptation of previously P-gp-negative cells or by selection of drug-resistant P-gp-positive clones. Elimination of such cells during initial treatment or at the time of recurrence is necessary to achieve cancer "cures". However, several P-gp inhibitors, such as verapamil and PSC833, all showed disappointing results in clinical trials and did not achieve survival benefit [27,32,33]. Alternative approach to overcome drug resistance is needed. Thus, the positive correlation between P-gp expression and oxaliplatin activity suggests a new individualized treatment strategy to overcome MDR in cancer. We can use oxaliplatin to target high levels of P-gp expression in recurrent tumors with MDR or tumors which constitutively express high levels of P-gp in patients with colorectal cancer.

Further studies are needed to further confirm such result using cancer cell lines expressing various levels of P-gp as a result of selection by drug exposure or by transfection with the ABCB1 gene, combined with a variety of methods that modulate P-gp function, i.e., using either P-gp inhibitors or RNA interference (RNAi). The mechanisms of P-gp-

mediated sensitization of oxaliplatin also need to be investigated. A future structure-activity relationship study would be helpful to understand the chemical principles that determine P-gp-oxaliplatin interaction. By identifying how an efflux transporter conveys sensitivity for oxaliplatin, these studies will lay a solid foundation in discovering a novel approach to overcome drug resistance and improve individualized cancer therapy in colorectal cancer and possibly other types of cancer. Since combination therapy is commonly used for CRC chemotherapy, the interactions between each of the agents in the regimen and P-gp need to be considered. According our results, the rationale would be to combine oxaliplatin with P-gp substrate drugs due to their opposite relationship with the P-gp.

In conclusion, we conducted a functional evaluation of a novel transporter-drug interaction obtained using a pharmacogenomic approach. Since relapsed tumors of patients after treatment with P-gp substrate drugs frequently display an MDR phenotype and P-gp overexpression, treatment by oxaliplatin or other drugs with positive P-gp-correlations may offer a new opportunity to overcome drug resistance. In addition, for the use of these drugs, screening for a P-gp overexpression, as a predictor of drug responsiveness, might be of clinical value. If such finding is validated by functional assays and future clinical studies, improvement in the therapeutic approach, e.g., predicting individual drug effect can be made possible.

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