ABSTRACT:

PLX, paclitaxel; P-gp, P-glycoprotein; PSC833, 6-[(2-((4-cyclosporin D; R)],6,4-E,4-S)-4-methyl-2-(methylamino)-3-oxo-6-octenoic acid
carbamidemethycyclooctatetraene; MDR, multidrug resistance; IL, interleukin; rIL, recombinant interleukin; HPLC, high-performance liquid chromatography; MIU, Million International Unit; LLC, Lewis lung carcinoma; RP, reverse phase; IS, internal standard; LLOQ, lower limit of quantification; C_{max}, maximal concentration; T_{max}, time of the maximal concentration; AUC, area(s) under the curve; NF, nuclear factor; JAK, Janus tyrosine kinase.

Among the presently used anticancer drugs, paclitaxel (PLX), a member of the taxane family, is one of the most effective agents developed in the past 3 decades. PLX has shown strong activity in the treatment of breast, ovarian and non-small cell lung cancer (Huizing et al., 2003). On the other hand, it has been shown that P-gp is expressed at the apical side of alveolar epithelial cells and lung vascular endothelium, suggesting that P-gp could play a role in drug transport from interstitium to lumen (van der Deen et al., 2005). In vivo, P-gp expression may be increased by the administration of cyclosporine and PLX results in enhanced oral bioavailability of PLX due to increased intestinal absorption (Kimura et al., 2002). P-gp inhibitors such as cyclosporine, PSC833, or GF120918 have been used in combination with anticancer drugs (P-gp substrates) to overcome the multidrug resistance (MDR) phenotype. The coadministration of cyclosporine and PLX results in enhanced oral bioavailability of PLX due to increased intestinal absorption (Kimura et al., 2002). However, P-gp inhibitors appear to be too toxic for routine use (Gallo et al., 2003). On the other hand, it has been shown that P-gp is expressed at the apical side of alveolar epithelial cells and lung vascular endothelium, suggesting that P-gp could play a role in drug transport from interstitium to lumen (van der Deen et al., 2005). Although P-gp has been characterized in several cell types in lung tissue, its effect on drug pharmacokinetics is not clear (Scheffer et al., 2002). Patients diagnosed with cancer who are in a state of a primary
immunosuppression, specifically, a lymphopenia or a deficit in endogenous production of interleukin (IL)-2, respond poorly to chemotherapy (Cereya et al., 2001). Also, long-term survival of patients with small cell lung cancer is correlated with IL-2 secretion at diagnosis, with long-term survival and complete response to chemotherapy only observed in patients with high IL-2 secretion at diagnosis (Fischer et al., 2000). In patients diagnosed with gastric cancer, perioperative immunotherapy with IL-2 corrects the postsurgical immune deficit and increases survival (Romano et al., 2004). Indeed, the IL-2 group showed lower post surgical complications (p < 0.05) and higher lymphocyte infiltration into the tumor (p < 0.001). Moreover, disease free survival was longer in the IL-2 group than in the control group, although these findings were not statistically significant (p < 0.06).

Recombinant interleukin (rIL)-2 is already used in the treatment of metastatic renal adenocarcinoma. It has been shown that rIL-2 decreases MDR1 mRNA and P-gp expression in human colon carcinoma cultured cells (Stein et al., 1996) and in intestine and brain of Swiss mice (Bonhomme-Favre et al., 2002). Furthermore, we have shown previously that rIL-2 decreases rhodamine transport through the reversed gut sac of Swiss mice (Veau et al., 2002). In addition, rIL-2 pretreatment increased PLX efficacy measured by the significant decrease of s.c. tumor growth and lung metastasis number in the Lewis lung carcinoma model (Hosten et al., 2006).

The aim of the present study was to document the pharmacokinetics of PLX in plasma and tissues after rIL-2 pretreatment in the Lewis lung carcinoma model after oral and i.v. administration and to investigate the effect of rIL-2 pretreatment on the intestinal and lung P-gp expression in mice by Western blot analysis.

Materials and Methods

Chemicals. Cell culture media and reagents were purchased from Invitrogen (Carlsbad, CA). PLX (Taxol) (paclitaxel powder from Taxus yunnanensis; Sigma-Aldrich, Saint-Quentin Fallavier, France) was diluted in methanol to obtain a stock solution (1 mg/ml). Docetaxel (Taxotere) (Sigma-Aldrich) was diluted in methanol to obtain a stock solution (1 mg/ml). Throughout the study, acetonitrile, triethylamine, hexane, ammonium acetate, ethyl acetate, and methanol (HPLC grade) were purchased from VWR (Fontenay sous Bois, France). Recombinant Proleukin, rIL-2, was purchased from Chiron (Suresnes, France). Recombinant IL-2 was reconstituted, and 1 ml was diluted with 5% dextrose solution to obtain a final concentration of 1.8 MIU/ml. PLX was extracted from 100 mg of weighed lung tissue or s.c. tumors. For analysis, the tissue samples were mixed with 100 ml of docetaxel [internal standard (IS)]. The mixture was vortexed for 20 s. Sample extraction was accomplished using SPE cyan 1-ml Bond Elut cartridges (Interchim, Fontenay sous Bois, France). Cartridges were washed using 1 ml of water and 1 ml of 20% methanol in 0.01 M ammonium acetate solution, followed by 1 ml of n-hexane. The cartridges were then dried under vacuum for 2 min. PLX and the IS were then eluted using 2 ml of triethylamine (0.1%) in acetonitrile. The eluent was evaporated under a gentle stream of nitrogen at 30°C. The residue was reconstituted in 100 ml of a water/acetonitrile mixture [1:1 (v/v)] and vortexed for 20 s. An aliquot of 50 ml was then injected into the chromatographic system.

Chromatographic analysis was achieved on a Nucleosil C18 column (4.6 × 250 mm, 5-µm i.d.) (Interchim) with a mobile phase composed of acetonitrile and water [1:1 (v/v)] delivered at a flow rate of 1.2 ml/min. The eluent was monitored at 227 nm. The quantification method was validated according to the Food and Drug Administration recommendations (Shah et al., 2000).

The PLX standard curve was correctly described by unweighted least-square linear regression. Over the PLX plasma concentration range of 50 to 5000 ng/ml, the determination coefficient (R2) of the calibration curves remained >0.99. Based on quality control samples, the overall relative S.D. (an index of precision) was less than 12%. The overall relative error (an index of accuracy) was less than 10%. The lower limit of quantification (LLOQ) was 50 ng/ml. The stability of plasma samples at −20°C was confirmed by analyzing six quality control samples at the end of the study.

PLX quantification in lung tissues and s.c. tumors. PLX tissue concentrations were measured using a validated RP-HPLC/UV method using modifications of the HPLC procedure described by Mohamed et al. (2003). Calibration standards of PLX were prepared in drug-free lung tissues from C57BL/6 mice by spiking with concentrated standards to obtain a concentration range between 100 to 10,000 ng/g. Quality control samples for PLX were prepared in drug-free lung tissues from C57BL/6 mice by spiking with concentrated standards. Three quality controls were prepared, low (600 ng/g), medium (4000 ng/g), and high (9000 ng/g). PLX tissue concentrations were measured using an RP-HPLC/UV method. This quantification followed a liquid/liquid extraction. PLX was extracted from 100 mg of weighed lung tissue or s.c. tumor. For analysis, the tissue samples were mixed with 100 µl of docetaxel (2 µg/ml) (IS) and 400 µl of acetonitrile. The mixture was vortexed for 20 s and centrifuged (10,000 rpm/min). The supernatant was evaporated under nitrogen at 30°C. The residue was reconstituted in 200 µl of water and mixed with 3 ml of ethyl acetate.

The mixture was agitated for 20 min and evaporated under nitrogen at 30°C. Mobile phase was then added, 100 µl of acetonitrile/water [48.52 (v/v)] and the sample was vortexed for 20 s. An aliquot of 50 µl was then injected into the chromatographic system.

Chromatographic analysis was performed on a Nucleosil C18 column (4.6 × 125 mm, 3-µm i.d.) (Interchim) with a mobile phase composed of acetonitrile and water [48.52 (v/v)], delivered at a flow rate of 1.2 ml/min with monitoring at 227 nm. Food and Drug Administration recommendations were followed to validate this method (Shah et al., 2000).

The standard curve of PLX was well described by 1/X2−weighted least-square linear regression (X = concentration). Over the PLX tissue concentration range of 100 to 10,000 ng/g, the determination coefficient (R2) of the calibration curves remained >0.99. The LLOQ was 100 ng/g. The precision
Fig. 1. Mean PLX concentration versus time profiles in plasma. Diamonds, PLX treatment alone i.v. at 4 mg/kg. Squares, PLX (i.v.) at 4 mg/kg after 3 days of pretreatment with rIL-2 administered i.p. at 0.27 MIU twice a day. Triangles, PLX alone p.o. at 15 mg/kg. Crosses, PLX (p.o.) at 15 mg/kg after 3 days of pretreatment with rIL-2 administered i.p. at 0.27 MIU twice a day. Data represent the mean PLX concentration ± S.E.M. in plasma (n = 3–4 per time point).

AUC sub 0 to sub t = 0.5 · (t sub 1 - t sub 0) · y sub 0 + \sum_{i=2}^{n} [0.5 · (t sub i - t sub i-1) · y sub i-1] + 0.5 · (t sub n - t sub n-1) · y sub n

(1)

SE sub AUC sub t = \sqrt{[0.5 · (t sub 1 - t sub 0) · SE sub t sub 0]² + \sum_{i=2}^{n} [0.5 · (t sub i - t sub i-1) · SE sub t sub i-1]² + [0.5 · (t sub n - t sub n-1) · SE sub t sub n]²}

(2)

Where y, and SE, are the mean placlitaxel concentration and its S.E. at time i (i = 0, 1, 2, n). The test for equality of the mean AUC between treatments A and B is performed using the standard Wald statistic:

Z sub abs = (AUC sub A - AUC sub B) / \sqrt{SE sub AUC sub A + SE sub AUC sub B}

(3)

Under the null hypothesis, which indicates that AUC are equal, this statistic follows a normal distribution. The null hypothesis is rejected if Z sub abs is greater than 1.96.

Western blot studies. In the Western blot analysis of the P-gp expression, the mean P-gp/β actin ratio was compared using the Student’s t test. The P-gp expression was expressed as the mean P-gp/β actin ratio ± S.E.M. (n = 4). The Student’s t test was used to compare the results obtained with or without rIL-2 pretreatment.

Results

Noncompartmental Analysis in Plasma after Oral and i.v. Administration. The plasma PLX concentration versus time profiles observed after oral and i.v. administration are shown in Fig. 1. The main pharmacokinetic parameters observed in plasma after oral and i.v. administration were obtained after a noncompartmental analysis, as summarized in Table 1. The plasma PLX maximal concentration (C max) in the rIL-2 + PLX group was 2.6-fold higher than in the PLX alone group after oral administration (p < 0.01). The plasma PLX total exposure, measured by AUC, was 3-fold higher in the rIL-2 + PLX group as compared with the PLX-alone group after oral admin-

<p>| TABLE 1 |</p>
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<th>PLX pharmacokinetic parameters in plasma compartment after p.o. 15 mg/kg and i.v. 4 mg/kg administration obtained from the noncompartmental analysis</th>
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**p < 0.01 (Student’s t test).**

***p < 0.001 (Bailer’s method).
istration (p < 0.001). After i.v. administration, plasma PLX $C_{\text{max}}$, AUC, and the terminal half-lives in the two groups were not significantly different.

**Noncompartmental Analysis in Lung Tissues.** The lung PLX concentration versus time profiles observed after oral and i.v. administration are shown in Fig. 2. The main pharmacokinetic parameters in lung tissue observed after oral and i.v. administration were obtained with a noncompartmental analysis as summarized in Table 2. After oral administration, PLX $C_{\text{max}}$ in the rIL-2 + PLX group was 1.6-fold higher as compared with the PLX-alone group. However, after i.v. administration, PLX $C_{\text{max}}$ was unchanged between the two groups. A prolonged PLX terminal half-life (8.3 versus 1.7 h in the rIL-2 + PLX and PLX-alone groups, respectively) and a significant 2.6-fold increase in the PLX AUC$_{0 \rightarrow \text{last}}$ was observed in the rIL-2 + PLX group as compared with the PLX-alone group ($p < 0.001$) after PLX oral administration. A prolonged terminal half-life (5.3 versus 1.7 h in the rIL-2 + PLX and PLX-alone groups, respectively) was also observed in the rIL-2 + PLX group after i.v. administration, whereas the AUC$_{0 \rightarrow \text{last}}$ was not significantly different. After oral administration, the AUC$_{\text{lung}}$ $0 \rightarrow \infty$/AUC$_{\text{plasma}}$ $0 \rightarrow \infty$ ratio in the PLX-alone group was 11.3 versus 12.7 in the rIL-2 + PLX group. After i.v. administration, this ratio was 2.6 in the PLX-alone group versus 3.5 in the rIL-2 + PLX group.

**Noncompartmental Analysis in s.c. Tumors.** The s.c. PLX concentration versus time profiles observed after oral and i.v. administration are shown in Fig. 3. The main pharmacokinetic parameters observed in s.c. tissue after oral and i.v. administration were obtained with a noncompartmental analysis as summarized in Table 3. After oral administration, PLX $C_{\text{max}}$ and AUC$_{0 \rightarrow \text{last}}$ in the rIL-2 + PLX group were increased by 2.1- and 3.41-fold, respectively, as compared with the PLX-alone group ($p < 0.01$). A prolongation of output half-life was also observed in the rIL-2 + PLX group as compared with the PLX-alone group (6.8 versus 2.69 h, respectively).

After i.v. administration, the PLX $C_{\text{max}}$ in the two groups was comparable with a prolonged output half-life (11.6 versus 4.9 h in the rIL-2 + PLX and PLX-alone groups, respectively). A significant 1.4-fold increase in AUC$_{0 \rightarrow \text{last}}$ was observed in the rIL-2 + PLX group as compared with the PLX-alone group ($p = 0.015$).

After oral administration, the AUC$_{\text{s.c. tumor}}$ $0 \rightarrow \infty$/AUC$_{\text{plasma}}$ $0 \rightarrow \infty$ ratios were 6.7 and 8.3 in the PLX-alone and rIL-2 + PLX groups, respectively. After i.v. administration, the same ratios were 2.6 and 4.8 in the PLX-alone and rIL-2 + PLX groups, respectively.

**Semiquantitative Determination of P-gp Expression by Western Blot Analysis in Intestine and Lung.** Western blot analysis of P-gp expression was performed on lung and intestine from four control mice and four mice treated with rIL-2 (16.5 µg twice a day) for 3 days. P-gp expression was significantly decreased in the lungs and intestine of the rIL-2-treated group as compared with the control group ($p < 0.05$) (Figs. 4 and 5).

**Discussion**

In this study, the effects of rIL-2 pretreatment on the plasma and tissue pharmacokinetics of orally and i.v. administered PLX were investigated in Lewis lung carcinoma bearing mice. The aim of these studies was to determine whether rIL-2 could optimize the pharmacokinetic properties of PLX in addition to its own antineoplastic properties.

Pretreatment with rIL-2 increased the plasma PLX AUC 3-fold and $C_{\text{max}}$ 2.6-fold after oral administration. In contrast, AUC and $C_{\text{max}}$ were unaffected by rIL-2 pretreatment when PLX was administered i.v. This result suggests an enhanced PLX intestinal absorption, resulting in an increased total exposure without altering its terminal half-life. The pharmacokinetic changes could be explained by either

**TABLE 2**

| PLX Pharmacokinetic Parameters in Lung Compartment after Oral 15 mg/kg and Intravenous 4 mg/kg Administration Obtained from the Noncompartmental Analysis |
|-----------------|-----------------|-----------------|-----------------|
|                 | Oral Administration | Intravenous Administration |
|                 | PLX Alone | PLX + rIL-2 | PLX Alone | PLX + rIL-2 |
| $T_{\text{max}}$ (h) | 2 | 2 | 0.25 | 0.25 |
| $C_{\text{max}}$ (ng/g) | 4092 ± 852 | 6688 ± 1074 | 4064 ± 304 | 3668 ± 635 |
| AUC$_{0 \rightarrow \text{last}}$ (ng/h/g) | 12,247 ± 2316*** | 32,571 ± 3794*** | 7798 ± 412 | 8989 ± 627 |
| AUC$_{\text{plasma}}$ (ng/h/g) | 15,355 ± 3235 | 35,678 ± 3807 | 8436 ± 416 | 9546 ± 635 |
| $t_{1/2}$ (h) | 1.70 | 8.70 | 1.65 | 5.28 |

*** $p < 0.001$ (Baird’s method).
an inhibition of cytochrome P450-mediated intestinal and hepatic PLX metabolism or by an inhibition of PLX transport via intestinal P-gp (Sonnichsen et al., 1995). PLX total exposure appeared to be unaffected by rIL-2 pretreatment after i.v. administration, suggesting that rIL-2 had no significant effect on hepatic PLX metabolism by cytochrome P450. Previous studies showed that rIL-2 administered i.p. at 0.27 MIU inhibited intestinal P-gp activity by decreasing intestinal P-gp functionality in mice (Veau et al., 2002). In addition, it has been demonstrated that the coadministration of PLX with a P-gp inhibitor (MS-209) (Naito et al., 2002) caused an increase of AUC and $C_{\text{max}}$ without modifying the other pharmacokinetic parameters (Kimura et al., 2002). Taken together, these findings suggest that rIL-2 inhibited intestinal P-gp functionality or expression without excluding an effect on cytochrome P-450. This hypothesis was strengthened by the intestinal Western blot analysis, which showed a significant decrease in intestinal P-gp expression in the rIL-2-pretreated group as compared with the control group.

The noncompartmental analysis of PLX lung data showed that rIL-2 pretreatment increased PLX AUC and $C_{\text{max}}$ after oral administration of PLX. No significant effect on total exposure or inlet of PLX administered i.v. was observed with rIL-2 treatment. PLX terminal half-life also appeared to be prolonged after rIL-2 pretreatment with either route of PLX administration. These results suggest that the increases in PLX AUC and $C_{\text{max}}$ after oral administration are probably related to higher PLX systemic exposure (plasma AUC) after rIL-2 pretreatment. The prolongation of PLX terminal half-life in lung observed in mice pretreated with rIL-2 could be the result of an inhibition of the expression or functionality of P-gp in lung. Indeed, the Western blot analysis of lung showed a significant decrease in lung P-gp expression in rIL-2-pretreated mice as compared with the control group. Two previous studies demonstrated the inhibition of P-gp function in lung. Campbell et al. (2003) showed that the coincubation of rat alveolar epithelial cell population with verapamil leads to inhibition of P-gp activity and to greater intracellular accumulation of P-gp substrate Rhodamine 123 during the efflux phase. In addition, Roerig et al. (2004) showed that the uptake of the P-gp substrate Rhodamine is increased in lung tissue in the presence of verapamil and GF120918 (P-gp inhibitors). In our study, rIL-2 pretreatment resulted in prolongation of PLX terminal half-life from lung after oral and i.v. administration of PLX, suggesting that rIL-2 inhibited P-gp expression or function in lung.

The noncompartmental analysis of PLX in s.c. tumors showed that rIL-2 pretreatment increased PLX AUC and $C_{\text{max}}$ after PLX oral administration. After i.v. administration of PLX, rIL-2 pretreatment led to a significant increase in PLX total exposure. PLX terminal half-life also appeared to be prolonged after rIL-2 pretreatment with either route of PLX administration. These results suggest that the increases in PLX AUC and $C_{\text{max}}$ after oral administration are probably related to higher PLX systemic exposure (plasma AUC) after rIL-2 pretreatment. Nevertheless, the increase of PLX total exposure and terminal half-life (regardless of the route of PLX administration) in s.c. tumors in mice pretreated with

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<td></td>
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<td>PLX Alone</td>
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<tr>
<td>$T_{\text{max}}$ (h)</td>
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<tr>
<td>$C_{\text{max}}$ (ng/g)</td>
<td>1612 ± 763</td>
<td>3373 ± 733</td>
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<td>$AUC_{0-\infty}$ (ng/h/g)</td>
<td>5746 ± 1185**</td>
<td>19597 ± 4673**</td>
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<tr>
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<td>23242 ± 4674</td>
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<td>$t_{1/2}$ (h)</td>
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** $p < 0.01$ (Bailer’s method).
* $p < 0.05$ (Bailer’s method).

**TABLE 3**

PLX pharmacokinetic parameters in s.c. tumor compartment after p.o. 15 mg/kg and i.v. 4 mg/kg administration obtained from the noncompartmental analysis
rIL-2 could be explained by other properties of rIL-2. Indeed, rIL-2 is known to induce capillary leak syndrome (Assier et al., 2005), meaning that rIL-2 may have increased vascular permeability and facilitated PLX penetration, especially in peripheral tissues. Moreover, it is well known that rIL-2 enhances the antitumor immune response, which decreases tumor growth and metastasis development in mouse tumor models (Taieb et al., 2006). PLX total exposure in the s.c. tumors may also be increased by rIL-2 by modifying the tumor cell density and the PLX distribution in the tumor, even when the systemic exposure to i.v. PLX was the same in the PLX and rIL-2 + PLX groups. However, if rIL-2 induced the capillary leak syndrome or anticancer effects, these hypotheses do not explain the PLX terminal half-life prolongation in s.c. tumors after rIL-2 pretreatment. Finally, rIL-2 could have decreased the P-gp expression or function in s.c. tumors, which may explain the prolonged PLX terminal half-life. However, the P-gp expression levels of the s.c. tumors were too low and variable as visualized by Western blot analysis to provide evidence for a significant decrease in P-gp expression induced by rIL-2 (data not shown).

In any event, the mechanism by which rIL-2 decreases P-gp expression may be explained by in vitro studies. Indeed, NF-κB and NF-AT (nuclear factor of activated T cells) are two nuclear transcription factors for IL-2 (Park et al., 2007). When IL-2 binds its receptor, it activates several proteins including Janus tyrosine kinase (JAK) and signal transducer and activator of transcription 1, 3, 5, and 6 (O’Sullivan et al., 2007). Signal transducer and activator of transcription 3, however, inhibits the antiapoptosis factor NF-κB (Hoentjen et al., 2005). A study has shown that NF-κB activates the orphan receptors pregnane X receptor/steroid and xenobiotic receptor, which induce the MDR1 gene transcription and P-gp expression. This study also reported that inhibition of NF-κB significantly reduces P-gp expression in HCT 15 cells (Bentires-Alj et al., 2003). Hence, by binding its receptor, rIL-2 could inhibit NF-κB (via STAT3 recruitment) and thus decrease the P-gp expression in vivo.

Oral administration of PLX has recently become a topic of great interest (Veltpamp et al., 2007). Indeed, oral treatment with cytotoxic agents is preferred because it reduces administration costs and facilitates the use of long-term treatment (Malingré et al., 2001). Treatment with anticancer drugs as PLX is limited by nonhematological and hematological toxicity, which is related to its systemic exposure (Gelderblom et al., 2002; Mielke et al., 2005). The present comparison between the two routes of administration provided evidence for two principle findings. The first, oral administration allowed the targeted tissues a much higher PLX exposure as compared with i.v. administration (AUCplasma 0 → a/AUCtissues 0 → a ratios were higher after oral administration as compared with the i.v. treatment). This result could be explained in part by the presence of Cremophor EL in the formulated PLX, which is not orally absorbed and may be responsible for the nonlinear pharmacokinetics of PLX after i.v. administration (van Tellingen et al., 1999). Indeed, after oral administration, when Cremophor is not present, plasma levels of PLX represent a higher fraction of free drug, which will result in enhancement of the availability of PLX to lung tissue and s.c. tumors. In contrast, after i.v. administration, entrapment of PLX in Cremophor EL micelles in the plasma compartment causes an increase of PLX affinity for this compartment (Veltpamp et al., 2007), which may decrease the PLX availability for lung tissue and s.c. tumors. Second, rIL-2 pretreatment allowed better PLX tissue penetration as compared with the PLX-alone group. The significant influence of rIL-2 on the PLX pharmacokinetics, combined with its intrinsic anticancer properties on tumor tissue in the Lewis lung carcinoma model, could represent an additional argument for therapeutic association of rIL-2 and orally administered anticancer drugs that act as efflux pump substrates.

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