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The Novel Anticancer Drug KRN5500 Interacts with, but is Hardly Transported by, Human P-Glycoprotein.

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The interaction of the novel anticancer drug KRN5500, a spicamycin derivative, with human P-glycoprotein (P-gp) was analyzed from the viewpoint of cellular pharmacokinetics, i.e. by means of [^{3}H] azidopine photoaffinity labeling, cellular accumulation and transcellular transport experiments. In this study, P-gp-overexpressing LLC-GA5-COL150 cells, porcine kidney epithelial LLC-PK$_1$ cells transformed with human *MDR1* cDNA, were used, since this cell line constructs monolayers with tight junctions, and would providae sufficient information for analyzing the cellular pharmacokinetics. 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay revealed that the growth-inhibitory effect of KRN5500 in LLC-GA5-COL150 cells was comparable to that in LLC-PK1 cells (IC_{50} = 79.4 and 72.7 nM, respectively), but the inhibition of [^{3}H] azidopine binding by KRN5500 was concentration-dependent in the membrane fraction of LLC-GA5-COL150 cells. The cellular accumulation of [^{14}C]KRN5500 after its

basal application in LLC-GA5-COL150 cells was slightly lower than that in LLC-PK_1 cells, and was restored by the multidrug resistance (MDR) modulator SDZ PSC 833. The basal-to-apical transport of [^{14}C] KRN5500 in LLC-GA5-COL150 cells was also slightly higher than that in LLC-PK_1 cells, and was inhibited by SDZ PSC 833. However, the basal-to-apical transport of [^{14}C]KRN5500 in LLC-GA5-COL150 cells was only a little higher than the apical-to-basal transport. Consequently, these results demonstrated that KRN 5500 interacted with, but was hardly transported via, P-gp. These observations suggested that KRN5500 may be useful even for the treatment of tumors exhibiting P-gp-mediated MDR.