In Vitro to In Vivo Comparison of the Substrate Characteristics of Sorafenib Tosylate toward P-Glycoprotein

M. J. Gnoth, S. Sandmann, K. Engel, and M. Radtke

Drug Metabolism and Pharmacokinetics, Bayer Schering Pharma AG, Wuppertal, Germany

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ABSTRACT:

Sorafenib (Nexavar) is a novel oral Raf kinase and vascular endothelial growth factor receptor inhibitor. Most anticancer drugs are substrates for ATP-binding cassette efflux pumps especially for P-glycoprotein (P-gp). To evaluate the influence of P-gp on the pharmacokinetics of sorafenib substrate properties for this transporter were investigated. Therefore, permeability of sorafenib across Caco-2 and P-gp-overexpressing cells was determined. To determine the in vivo relevance of these in vitro findings, pharmacokinetics of sorafenib in mdr1a/1b(−/−) and wild-type (WT) mice was studied. Sorafenib is highly permeable and exhibits a slight efflux across Caco-2 cells. In P-gp-overexpressing cells, a small concentration-dependent efflux was observed, which was completely blocked by the addition of ivermectin. In mdr1a/1b(−/−) and WT mice, unchanged compound represented by far the majority of radioactivity in plasma. After intravenous and oral administration, brain/plasma concentration ratios in mdr1a/1b(−/−) mice were 1.3- to 1.5-fold higher than those in WT mice. However, after intravenous or oral administration, plasma concentrations were similar in both mouse strains. In conclusion, sorafenib is highly permeable and a weak P-gp substrate in vitro. These findings were confirmed by the small factor of 1.3 to 1.5 observed for the brain/plasma ratios in mdr1a/1b(−/−) versus WT mice in vivo. Based on these in vitro and in vivo results, it is unlikely that P-gp has a major effect on the plasma concentrations of sorafenib in humans. Because of the high permeability and low P-gp-mediated transport, sorafenib might be able to cross the blood-brain barrier and target tumors within the brain.

Sorafenib tosylate (Nexavar) is a novel oral Raf kinase and vascular endothelial growth factor receptor (VEGFR) inhibitor that prevents tumor growth by combining two anticancer activities: inhibition of tumor cell proliferation and tumor angiogenesis. Sorafenib inhibits tumor cell proliferation by targeting the receptor tyrosine kinases VEGFR-2, VEGFR-3, and platelet-derived growth factor receptor and their associated signaling cascades (Lyons et al., 2001). Sorafenib has shown marked clinical efficacy and safety in advanced renal cell and hepatocellular carcinoma (Kane et al., 2006; Escudier et al., 2007).

ATP-driven efflux pumps such as P-glycoprotein (P-gp) (MDR1 or ABCB1), multidrug resistance-associated protein 2 (ABCC2), and breast cancer resistance protein (ABCG2) can have a significant effect on chemotherapy. These proteins are localized at apical membranes of epithelial barriers and canicular membranes of hepatocytes, facilitating excretion of drugs via liver, intestines, and kidneys and limiting their distribution to tissues such as brain and testis (Borst and Elferink, 2002). Furthermore, overexpression of these transport proteins in tumor cells can lead to drug resistance (Gottesman and Pastan, 1993). At present, one of the best investigated efflux pumps is P-gp, a 170-kDa ATP-driven transport protein (Borst and Elferink, 2002) known to limit distribution of anticancer drugs to the brain and cancer cells (Schinkel et al., 1995; Dai et al., 2003). In addition, brain penetration and tumor exposure also depend on the permeability of the drug.

Therefore, the permeability of sorafenib was investigated in vitro using Caco-2 cells. Substrate characteristics of sorafenib toward P-gp were studied in vitro in more detail using LLC-PK1 cells overexpressing P-gp (L-MDR1 cells) (Schinkel et al., 1995).

It has been demonstrated that knockout mice are a good model to study the influence of transport proteins on the pharmacokinetics of drugs (Schinkel et al., 1995, 1997; Lagas et al., 2006). To evaluate the relevance of the in vitro findings for the in vivo situation brain and plasma concentrations of sorafenib in mdr1a/1b(−/−) and wild-type (WT) mice were determined. The well known P-gp substrate digoxin was used as a positive control to validate the in vivo model (Schinkel et al., 1997).

ABBREVIATIONS: VEGFR, vascular endothelial growth factor receptor; P-gp, P-glycoprotein; MDR/mdr, multidrug resistance; ABC, ATP binding cassette; WT, wild-type; TEER, transepithelial electrical resistance; DMSO, dimethyl sulfoxide; HPLC, high-performance liquid chromatography; B, basolateral; A, apical; KO, knockout; AUC, area under the curve.
Materials and Methods

Chemicals. [14C]Sorafenib was applied as the tosylate (99.6% radiochemical purity) and with a specific radioactivity of 4.24 MBq/mg. Trinitigated digoxin was purchased from PerkinElmer Life and Analytical Sciences (Waltham, MA) with a specific radioactivity of 11.84 MBq/mg. Ivermectin, ketoprofen, metoprolol, digoxin, and vinblastine were purchased from Sigma-Aldrich (Deisenhofen, Germany). Fluvasatin was purchased from Merck KGaA (Darmstadt, Germany). Cell culture materials were purchased from Invitrogen (Karlsruhe, Germany) unless otherwise stated. All other chemicals were reagent grade or better.

Culture of Caco-2 Cells. Caco-2 cells were purchased from DSMZ (the German Resource Centre for Biological Material, Braunschweig, Germany). Cells were seeded at a density of 4 × 103 cells/well on 24-well polycarbonate insert plates, 0.4-μm pore size (Corning Life Sciences, Lowell, MA) and maintained for 15 days in Dulbecco’s modified Eagle’s medium’s supplemented with 10% fetal bovine serum albumin, 20 mM glucose, 10 mg/500 ml streptomycin, and 10,000 IU/500 ml penicillin in a humidified incubator at 8% CO2. The medium was changed twice a week.

Culture of L-MDRI Cells. LLC-PK1 cells overexpressing P-glycoprotein (L-MDRI) cells were kindly provided by Dr. A. Schinkel (Netherlands Cancer Institute, Amsterdam, The Netherlands) (Schinkel et al., 1995). For flux studies cells were seeded at a density of 2 × 105 cells/well on 24-well polycarbonate insert plates, 0.4-μm pore size, and grown for 4 days in medium 199 supplemented with 2 mM L-glutamine, 10% fetal bovine serum, 10 mg/500 ml streptomycin, and 10,000 IU/500 ml penicillin in a humidified incubator at 5% CO2 with a medium change every 2 to 3 days.

Cellular Flux Studies. Before running the assay culture medium was replaced by transport buffer consisting of Hanks’ balanced salt solution buffer (pH 7.4) supplemented with 10 mM HEPES and 20 mM glucose (only for Caco-2 cells). The acceptance criteria for acceptable batches of cell monolayers were a transepithelial electrical resistance (TEER) value of 600 Ω. Stock solution of [14C]sorafenib tosylate was prepared in DMSO and diluted 100-fold with transport buffer. For inhibition studies, iverecin was added at defined concentrations to the stock solution.

These solutions were applied either to the apical or basal compartment, and 1% DMSO was added to the buffer in the trans-compartment. Because of the high nonspecific binding of sorafenib to plasticware, the assay was started after a 1-h preincubation to ensure equilibrium and saturation of nonspecific binding. After a 1-h preincubation at 37°C, an aliquot of the cis-compartment was taken. The solution of the trans-compartment was removed and washed with phosphate-buffered saline and fresh transport buffer was added. After a 2-h incubation at 37°C, samples were taken from both compartments. Furthermore, the trans-compartment was washed with methanol to recover any compound bound to plastics. All samples from the trans-compartment were pooled and analyzed by liquid scintillation. To determine the amount of compound already present in the trans-compartment after the 1-h preincubation, a parallel experiment was run and terminated after 1 h. The trans-compartment was washed with phosphate-buffered saline and rinsed with methanol. These samples were analyzed by liquid scintillation counting. The 2-h trans values were corrected for the amount of drug permeated during the preincubation.

Measurement of TEER. TEER was measured in Hanks’ balanced saline solution buffer before and after the transport studies using a STX 100 TEER electrode (World Precision Instruments, Berlin, Germany). To ensure the integrity of the cell monolayer TEER values were determined before and after the experiment.

Analysis of Reference Compounds. Samples were analyzed by high performance liquid chromatography (HPLC)-tandem mass spectroscopy on an API3000 system (AB Sciex, Darmstadt, Germany) using a Purospher star column. The eluent was 10 mM ammonium acetate buffer, pH 3.0. Compounds were eluted using a gradient from 20 to 90% acetonitrile in 2 min. For the calculation of apparent permeability (Papp) values peak heights or peak areas were used. No difference was observed for Papp values when data were compared with Papp values calculated based on concentrations (data not shown).

Calculation of Papp Value and Efflux Ratio. The Papp was calculated using the following equation: Papp = (Vr/Po)(1/US)(P/2t), where Vr is the volume of medium in the receiver chamber, Po is the measured peak height or peak area of the test drug in the donor chamber at t = 0, S is the surface area of the monolayer, and t is the incubation time (2 h). The efflux ratio is defined by the following equation: efflux ratio = Papp(B-A)/Papp(A-B), where Papp(B-A) and Papp(A-B) represent the apparent permeability of test compound from the basolateral to apical and apical to basolateral side of the cellular monolayer, respectively.

Cell data are expressed as arithmetic means and S.D. The S.D. for the efflux ratio was calculated using linear error propagation.

In Vivo Animal Studies. Male FVB Tac-KO/mdrla(+/−)-KO/mdrb1 mice [mdrla(+/−)/−], P-gp double knockout and FVB wild-type [mdrla(+/−)/+], WT) mice of approximately 8 weeks were purchased from Taconic Farms (Germantown, NY). Animals were housed and handled according to institutional guidelines issued by the government of the Federal Republic of Germany (May 25, 1998, RGBI. 1 S. 1105, 18181).

Plasma and brain tissue were collected after a single intravenous bolus administration (0.5 mg/kg b.wt.) and single oral administration (0.5 and 4 mg/kg b.wt.) of [14C]sorafenib tosylate. For intravenous administration, [14C]sorafenib tosylate (2.13 MBq/kg) was formulated in plasma (1% DMSO + 99% plasma, v/v), 0.137 mg/ml, 5 ml/kg) and injected into the tail vein. For oral administration, [14C]sorafenib tosylate (2.13 MBq/kg) was dissolved in a NaCl-based formulation (5% ethanol + 25% PEG400 + 50% Tween 80 + 65% NaCl, v/v, 0.137 and 1.01 mg/ml, 5 ml/kg) and administered by gastric gavage. [3H]Digoxin (0.5 mg/kg) was administered intravenously into the tail vein at a single bolus dose (9.25 MBq/mg) using a formulation according to Leusch et al. (2002).

At dedicated time points after oral or intravenous administration, animals were sacrificed under deep isoflurane anesthesia, and blood samples were collected from the carotid artery. Blood cells and plasma were separated by centrifugation, and the plasma was stored at −20°C until radioanalytic analysis. Then, brain tissue was homogenized in 1000 µl of demineralized water (water) using a Potter technique (Wheaton Science International, Millville, NJ). Radioactivity was determined by liquid scintillation counting. To determine volatility of the [3H]radiolabel of digoxin, two aliquots of plasma and brain samples of mdrla(+/−)/−) and WT mice were freeze-dried, analyzed for total radioactivity, and compared with wet plasma and brain samples. In the present experiments, the [3H]radiolabel of digoxin was not volatile as the equivalent concentrations of total radioactivity in wet samples (unchanged compound, radioactive metabolites, and tritiated water) were confirmed in freeze-dried samples (removed tritiated water).

Calculation of Brain/Plasma Ratio of mdrla(+/−)/− versus WT Mice. To describe the impact of P-gp on drug distribution in brain, the ratio of brain to plasma equivalent concentrations was calculated in mdrla(+/−)/−) and WT mice. Finally, the ratio of the brain/plasma ratios of mdrla(+/−)/−) (KO) and WT [brain/plasma ratio mdrla(+/−)/−)/brain/plasma ratio WT] was calculated: ratio of the brain/plasma ratio KO/WT = (brain/plasma ratio KO)/(brain/plasma ratio WT).

In addition, the area under the curve (AUC) of total radioactivity in plasma and brain of mdrla(+/−)/−)/−) (KO) mice was calculated from samples at 0.5, 1, 2, and 4 h after dosing and was compared with those of WT mice after intravenous administration.

Radioanalysis. Radioactivity of liquid samples was measured by liquid scintillation counting with automatic quench correction by the external standard channel ratio method at 13°C using Ultima Gold as scintillation cocktail (Packard Instruments BV, Groningen, The Netherlands). Counting time (1–30 min) for radioactivity determination was chosen according to the respective radioactivity concentration of the sample. The equivalent concentrations were calculated from the radioactivity concentrations (megabecquerels per milliliter) in the respective samples, applying the molecular weight and the specific radioactivity (4.24 MBq/mg) of sorafenib tosylate.

Metabolic Profiling of Plasma. Metabolite patterns in plasma samples were determined using HPLC with off-line radioactivity detection. Sorafenib and its metabolites were quantified using radioactivity in combination with the specific activity of [14C]sorafenib. Each HPLC run was split every 10 s into fractions (83 µl, due to a flow through the column of 0.5 ml/min), and the radioactivity of each fraction was determined by liquid scintillation counting (Wallac 1450 Microbeta Plus, Freiburg, Germany). To detect potential metabolites plasma samples of WT or mdrla(+/−)/−) mice were pooled (50 µl,
RESULTS

Bidirectional Flux Studies across Caco-2 Cells. [$^{14}$C]Sorafenib showed $P_{app}$ values for the apical to basolateral direction of 16.4 ± 1.1 and 33.5 ± 16.3 × 10⁻⁶ cm/s at 0.1 and 1 μM, respectively (Table 1). Sorafenib $P_{app}$ values were in the range of the $P_{app}$ values for ketoprofen (26.5 ± 6.7 × 10⁻⁶ cm/s), metoprolol (32.5 ± 2.4 × 10⁻⁶ cm/s), and fluvastatin (17.5 ± 2.0 × 10⁻⁶ cm/s) (Table 1). The low-permeability compound atenolol showed a significantly lower permeability of 0.66 ± 0.048 × 10⁻⁶ cm/s (Table 1). The known P-gp substrate digoxin showed a low permeability from A to B of 0.37 ± 0.055 × 10⁻⁶ cm/s and efflux ratio of 59 (Table 1). For sorafenib small efflux ratios of 4.7 ± 3.7 to 2.5 ± 1.2 were observed at concentrations of 0.1 and 1 μM, respectively (Table 1).

Bidirectional Flux Studies across L-MDR1 Cells. Active efflux was investigated in more detail by determining bidirectional permeability of [$^{14}$C]sorafenib across P-gp-overexpressing L-MDR1 cell monolayers. Efflux ratios of sorafenib were 6.8 ± 2.0 and 4.3 ± 1.5 at 0.1 and 1 μM, respectively (Table 2). The efflux ratio decreased to 1.3 ± 0.6 by the addition of 5 μM ivermectin, a known P-gp inhibitor (Schwab et al., 2003). Digoxin (25 μM) and vinblastine (2 μM) showed efflux ratios of 12 ± 3.5 and 37 ± 8.8, respectively.

Brain Penetration of Digoxin in mdr1a/1b(−/−) Knockout Mice. To further evaluate the influence of P-gp on the pharmacokinetics of sorafenib, especially distribution into the brain, in vivo studies in mdr1a/1b(−/−) and WT mice were performed. The mdr1a/1b(−/−) mouse model was validated using digoxin, a strong P-gp substrate (Schwab et al., 2003; Schinkel et al., 1997). Four hours after intravenous administration digoxin concentrations in plasma and brain were 1.8- and 39-fold higher in KO mice compared with WT mice (Table 3). Not only the distribution into the brain was affected by the knockout of P-gp but also plasma concentrations were elevated. Thus, it is more appropriate to compare the quotient of brain/plasma ratios in knockout and WT mice. Digoxin showed a quotient of 23 for the brain/plasma ratios 4 h after administration in KO versus WT mice (Table 3).

Metabolic Pattern of Sorafenib in mdr1a/1b(−/−) and WT Mice. When total radioactivity is used to determine brain and plasma concentrations of sorafenib, it is a prerequisite to demonstrate that sorafenib represents the vast majority of circulating radioactivity. Metabolic patterns in mdr1a/1b(−/−) and WT mice were investigated up to 4 h after intravenous administration and also 1 and 4 h after oral administration of [$^{14}$C]sorafenib tosylate. In the time interval 0.5 to 4 h after intravenous administration, unchanged compound accounted for 85% to 90% of the radioactivity.
for 95 to 99% of the radioactivity present in plasma (Table 4). One hour after oral administration of 0.5 and 4 mg/kg [14C]sorafenib to male mdr1a/1b(−/−) (○, △) or WT (●, ▲) mice (n = 3 animals/time point), *, statistically different, p < 0.05.

**Brain Penetration and Plasma Concentrations of Sorafenib in mdr1a/1b(−/−) and WT Mice.** Whole brain concentrations in mdr1a/1b(−/−) mice 1 h after intravenous administration of 0.5 mg/kg [14C]sorafenib tosylate were statistically higher (p < 0.05) and showed a tendency toward higher concentrations at the other time points investigated compared with those in the WT mice (Fig. 1). In whole brain, the concentrations reached 10 to 20% and 8 to 16% of the plasma concentrations in mdr1a/1b(−/−) and WT mice, respectively. AUCs of total radioactivity were 96 µg-Eq · h/l in brains of WT mice and 133 µg-Eq · h/l in brains of mdr1a/1b(−/−) mice. The corresponding AUCs of total radioactivity were 1050 µg-Eq · h/l in plasma of WT mice and 1038 µg-Eq · h/l in plasma of mdr1a/1b(−/−) mice after intravenous administration.

Thus, radioactivity associated with [14C]sorafenib was clearly entering the brain. Differences in the distribution patterns between mdr1a/1b(−/−) and WT mice are best reflected by comparison of the respective brain/plasma ratios. Brain/plasma ratios in mdr1a/1b(−/−) were slightly higher (1.3-fold) than those in WT mice (Table 5).

Distribution of radioactivity into the brain was also investigated 1 h and 4 h after oral administration of 0.5 and 4 mg/kg [14C]sorafenib tosylate. Plasma concentrations were not affected by the knockout of P-gp (Fig. 2A). In contrast with the plasma concentrations, a slight increase of brain concentrations was observed (Fig. 2B). One hour after oral administration, for both the 0.5 and 4 mg/kg the brain/plasma ratio was 0.053 in WT mice. In mdr1a/1b(−/−) mice, brain/plasma ratios were slightly higher, amounting to 0.068 to 0.078 for the 0.5 and 4 mg/kg dose, respectively. Four hours after oral administration of 0.5 or 4 mg/kg brain/plasma, ratios increased in WT as well as in mdr1a/1b(−/−) mice amounting to 0.075 and 0.11 (WT) and 0.11 to 0.12 [mdr1a/1b(−/−)], respectively.

Brain/plasma ratios of mdr1a/1b(−/−) at the respective time points were 1.3- and 1.5-fold higher than those in WT mice, confirming the ratio of 1.3 observed after intravenous dosing (Table 5). Only 4 h after oral administration of 0.5 mg/kg [14C]sorafenib tosylate no difference in the brain/plasma ratio was observed.

**Discussion**

In this article, the in vitro permeability and substrate characteristics of sorafenib toward P-gp are described. Furthermore, in vitro findings were compared with results from in vivo studies in mdr1a/1b(−/−) mice. One prerequisite for an effective anticancer treatment is good permeability. According to the Food and Drug Administration guidelines for the Biopharmaceutics Classification System of new chemical entities, the P<sub>app</sub> value has to be compared with 20 reference compounds for which the fraction of dose absorbed in human is known. Comparison of sorafenib at 1 µM revealed a permeability coefficient that is similar to ketoprofen, metoprolol, and fluvastatin, all classified as highly permeable (Food and Drug Administration). Thus, sorafenib was also classified as highly permeable. Sorafenib showed an efflux ratio of >2 in Caco-2 cells. Compared with other substrates for efflux pumps such as digoxin (Balimane et al., 2004), paclitaxel (Taxol) (Crowe, 2002), or vinblastine (Tang et al., 2002), all showing efflux ratios higher than 10, the observed efflux ratio in Caco-2 cells for sorafenib was low.

In P-gp-overexpressing L-MDR1 cells an efflux was observed that was completely blocked by the addition of ivermectin, a strong P-gp inhibitor (Schwab et al., 2003), demonstrating that sorafenib is a P-gp substrate. The efflux of sorafenib across L-MDR1 cells was significantly reduced at higher concentrations, which might be a hint for a saturable transport (Table 2). With regard to maximal sorafenib plasma concentrations of 6.3 µM (Richly et al., 2006) after oral administration of 400 mg b.i.d. (therapeutic dose), the P<sub>app</sub>-mediated transport of sorafenib in patients might be saturated. Compared with digoxin, vinblastine (Table 2), and paclitaxel (efflux ratio of 108) (Varma et al., 2005), for which an in vivo effect of P-gp on the pharmacokinetics has been shown (Schinkel et al., 1994, 1995; van Asperen et al., 1998), sorafenib showed a lower efflux ratio in L-MDR1 cells. Summarizing the in vitro findings, with regard to its efflux ratio sorafenib is classified as a weak P-gp substrate. Although the observed efflux and high permeability suggest that P-gp would be expected to have only a minor effect on the pharmacokinetics of sorafenib, it is important to confirm these findings in an in vivo experiment.

Transgenic mice lacking mdr1a/1b genes and proteins have been generated to get a better understanding of the physiological function of P-gp and its influence on the pharmacokinetics of transported drugs.
To further investigate the effect of P-gp pharmacokinetics, especially the effect on plasma concentrations and brain penetration of sorafenib, studies in mdr1a/1b knockout mice were performed. The model was validated using [3H]digoxin, a well characterized P-gp substrate (Mayer et al., 1996; Kawahara et al., 1999). The observed increase of radioactivity in plasma and brain of KO mice compared with WT mice is in good accordance with earlier publications reporting a 27- and 2.9-fold increase in brain and plasma concentrations, respectively (Schinkel et al., 1994, 1997). Thus, the in vivo setup applying WT and KO mice that we used was considered to be a suitable model to investigate the impact of P-gp on the pharmacokinetics, especially distribution to the brain.

As a next step, plasma and brain concentrations of [14C]sorafenib in WT and mdr1a/1b(-/-) mice were determined after oral and intravenous administration at several time points. For these studies, radioactively labeled compound was used. To ensure that radioactivity reflects the concentrations of the parent compound, a metabolic profile was determined. The majority of radioactivity in plasma was associated with parent compound, indicating that total radioactivity reflects the concentrations of sorafenib adequately. When whole brain homogenates were used to determine the distribution of a drug into the brain, the brain vascular space in mice, accounting for approximately 1.5% (Murakami et al., 2000; Dai et al., 2003) of the whole brain volume, should be taken into account. However, this is only relevant for compounds with a low central nervous system penetration. Brain concentrations for sorafenib in WT and KO mice were higher than 8%, relating to the plasma concentrations at all time points, indicating that sorafenib is crossing the blood-brain barrier. This is also reflected by the fact that plasma and brain concentration time curves show the same slope and therefore belong to the same compartment.

For both routes of administration, plasma concentrations and AUCs (intravenous only) of sorafenib in KO and WT were not different at any time point investigated, indicating that P-gp is unlikely to have a major influence on the absorption and excretion of sorafenib. Brain/plasma ratios of sorafenib in KO mice were 1.3-fold higher than those in WT mice. When this small increase after the knock out of P-gp is compared with that after other substrates such as vinblastine (5.5-fold) (Schinkel et al., 1994), imatinib (7-fold) (Dai et al., 2003), and digoxin (9.6-fold) (Schinkel et al., 1997), the observed increase for sorafenib seems to be of minor relevance. These compounds also showed significantly higher plasma concentrations in KO mice than in WT mice, which was not observed for sorafenib. Thus, sorafenib is a weak P-gp substrate in vivo, confirming the in vitro findings. Nevertheless, of the few time points it seems to be appropriate to translate these observations into an estimation of the effects of P-gp on the pharmacokinetics of sorafenib.

The clinical relevance of the in vitro and in vivo findings as described in this article has been demonstrated by other groups. Using cells overexpressing mouse and human P-gp paclitaxel was classified as a strong substrate (Schellens et al., 2000; Bardelmeijer et al., 2002). These findings were confirmed using mdr1a/1b(-/-) mice (Lagas et al., 2006) and WT mice cotreated with the P-gp inhibitor cyclosporin A (van Asperen et al., 1998), which showed significantly higher
plasma and brain concentrations compared with those of control animals. In clinical studies, paclitaxel plasma concentrations with or without coadministration of cyclosporin A were significantly higher in the cotreated group (Meerum Terwogt et al., 1999). Thus, results from mice can reflect the clinical situation in humans (Schellens et al., 2000).

Based on these in vitro and in vivo findings, it is unlikely that P-gp is affecting the plasma concentrations of sorafenib in humans and most likely will not limit the entry of sorafenib into the brain or cancer cells. The high permeability of sorafenib tosylate and low in vitro P-gp transport rates might be beneficial with respect to treatment of central nervous system tumors.

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Address correspondence to: Dr. Mark Gnoth, Bayer Schering Pharma AG, Global Drug Discovery, Drug Metabolism and Pharmacokinetics, Building 468, Aprather Weg 18a, D-42096 Wuppertal, Germany. E-mail: markjean.gnoth@bayerhealthcare.com

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