High Impact of Oatp1a/1b Transporters on In Vivo Disposition of the Hydrophobic Anticancer Drug Paclitaxel

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Abstract

Purpose: Organic anion-transporting polypeptides (OATP) mediate the cellular uptake of a broad range of drugs. The hydrophobic anticancer drug, paclitaxel (PTX), was recently identified as a substrate for OATP1B3 in vitro. We investigated the role of Oatp1a/1b transporters in the pharmacokinetics of PTX in vivo, as well as their impact at different dose levels of PTX and methotrexate (MTX).

Experimental Design: Recently generated Sko1a1b−/− (lacking all Oatp1a/1b transporters) and wild-type mice were intravenously dosed with 2, 10, or 50 mg/kg of PTX, or with 10, 50, or 500 mg/kg of MTX, and plasma and tissue drug concentrations were measured.

Results: In spite of its hydrophobicity, PTX systemic exposure (at 10 mg/kg) was increased by greater than 2-fold in Sko1a1b−/− mice compared with wild-type, whereas PTX liver uptake was reduced by about 2-fold. Oatp1a/1b transporters displayed a high impact on PTX and MTX pharmacokinetics over a broad dose range. For MTX, even at 500 mg/kg, saturation of Oatp1a/1b was not observed, with a 3.4-fold increase in plasma and 30-fold decrease in liver levels in Sko1a1b−/− mice compared with wild-type. Although beginning saturation of Oatp1a/1b was observed at the highest dose of PTX, plasma levels in Sko1a1b−/− mice were still 1.7-fold increased and liver levels 1.5-fold decreased compared with wild-type.

Conclusion: Oatp1a/1b transporters play a pronounced role in determining plasma levels and tissue distribution of MTX and PTX, thus affecting even highly hydrophobic drugs. Variation in OATP1A/1B transporter activity, due to genetic variation, inhibition, and/or tumor expression might affect toxicity and therapeutic efficacy of these anticancer drugs. Clin Cancer Res; 17(2); 294–301. ©2010 AACR.
The anticancer drugs, paclitaxel and methotrexate, are associated with sometimes severe, and even lethal, toxicity in patients. Paclitaxel has a narrow therapeutic window, and often leads to hypersensitivity, neutropenia, and neurotoxicity. Methotrexate toxicity (mucositis, renal and hepatic toxicity) has been correlated with plasma levels of the drug. Using Slco1a1b−/− mice, we here show a profound effect of the Oatp1a1b drug uptake transporters on the pharmacokinetics of paclitaxel and methotrexate over a broad range of dosages. The high impact of organic anion-transporting polypeptides (OATP) 1A1/1B on the hydrophobic drug, paclitaxel, was unexpected, as this drug was thought to mainly pass membranes by passive diffusion. Our results suggest that patients with polymorphisms in OATP1A1/1B transporters might be at increased risk of developing toxicity upon paclitaxel or methotrexate treatment. Tumor OATP1A/1B expression may also affect tumor drug sensitivity. In addition, inhibition of OATP1A1/1B transporters during chemotherapy by (pre)treatment with other drugs might affect drug toxicity and therapeutic efficacy.

European Caucasian population failed to demonstrate a link between genetic variants in SLCO1B3 and disposition of paclitaxel (PTX; ref. 8), another study associated an SNP in SLCO1B3 with leukopenia induced by the taxane docetaxel in Japanese patients (9). These clinical studies clearly demonstrate that polymorphisms in SLCO1A1/1B genes can contribute significantly to interindividual variation in disposition, toxicity, and therapeutic response for a wide range of drugs. It is therefore important to understand the relative roles of OATP1A1/1B transporters in drug pharmacokinetics in vivo, especially for anticancer drugs as these drugs often have narrow therapeutic windows. Our group recently generated and characterized a novel Oatp1a1b−/− transporter knockout mouse model (Slco1a1b−/− mice; ref. 10). As the various Oatp1a and Oatp1b transporters of both mouse and human display a large overlap in tissue distribution and substrate specificity, we generated a mouse model lacking all Oatp1a and Oatp1b transporters. Using these mice, we could show a pronounced role of Oatp1a1b transporters in the physiologic processes of bilirubin and bile salt distribution and disposition. Furthermore, the pharmacokinetics of some polar drugs (MTX and fexofenadine) was extensively characterized and tumor drug sensitivity was significantly up- or downregulated in the Slco1a1b−/− mice, which was not previously possible.

PTX is widely used in the treatment of breast and ovarian cancer, non–small cell lung cancer, and Kaposi’s sarcoma (11). In contrast to MTX and fexofenadine, PTX is a very hydrophobic drug that is thought to easily pass cell membranes by passive diffusion. It is therefore assumed that drug uptake transporters, like Oatp1a1b transporters, do not play an important role in the pharmacokinetics of PTX. Surprisingly, however, PTX was recently identified as a substrate of OATP1B3 in vitro (8, 12), although transport activity was low, and it was uncertain whether this would have significant impact in vivo.

The aim of this study was to elucidate the possible role of Oatp1a1b transporters in PTX disposition in vivo by using Oatp1a1b cluster knockout mice. We previously showed the value of knockout mice in studying the role of ABCB1 (P-glycoprotein, P-gp) and/or ABCC2 (multidrug resistance protein 2, Mrp2) in PTX pharmacokinetics (13, 14). We further aimed to better understand the impact of the Oatp1a1b transporters at different systemic exposure levels of the anticancer drugs PTX and MTX, by testing different dosages. MTX, for instance, is given at widely different dose ranges in the clinic, demonstrating the relevance of testing multiple dosages. Results of this study demonstrate that the impact of OATP1A1/1B transporters on the pharmacokinetics, tissue, and possibly also tumor distribution of hydrophobic drugs, like PTX, may have been underestimated so far.

Materials and Methods

Animals

Mice were housed and handled according to institutional guidelines complying with Dutch legislation. The animals used in this study were wild-type and Slco1a1b−/− (i.e., Oatp1a1b knockout) mice (10) of comparable mixed genetic background (~50% 129/Ola, 50% FVB) between 9 and 14 weeks of age. Oatp2b1, which is expressed in liver and intestine, and might have overlapping or compensatory functions with the Oatp1a1b proteins, was not significantly up- or downregulated in the Slco1a1b−/− mice as judged by RT-PCR (reverse transcriptase PCR; ref. 10). Animals were kept in a temperature-controlled environment with a 12-hour light/12-hour dark cycle. They received a standard diet (AM-II; Hope Farms) and acidified water ad libitum.

Chemicals and reagents

PTX was from Sequoia Research Products, MTX (100 mg/mL of Emthexate PF) from Pharmachemie, methoxyflurane (Metofane) from Medical Developments Australia, isoflurane (Forane) from Abbott Laboratories, and heparin (5,000 IE/mL) from Leo Pharma BV.

Plasma and tissue pharmacokinetic experiments

For intravenous dosage of PTX, the drug was formulated in ethanol and polysorbate 80 (1:1, v/v) at 1, 2, 6, or 30 mg/mL. This solution was diluted with saline for administration yielding final drug concentrations of 0.4 (2 mg/kg), 2 (10 mg/kg), and 10 mg/mL (50 mg/kg). Five microliters per gram of body weight was injected as single bolus into the tail vein of mice (n = 4–6 for each group). For intravenous
administration of MTX, the stock solution (100 mg/mL) was diluted with saline for administration of dose levels of 10 and 50 mg/kg, yielding final drug concentrations of 2 (10 mg/kg) and 10 mg/mL (50 mg/kg). For the dosage of 500 mg/kg, undiluted stock solution (100 mg/mL) was injected. Five microliters per gram of body weight was administered as single bolus into the tail vein of mice (n = 4–5 for each group). Animals were sacrificed at indicated time points by terminal bleeding through cardiac puncture under methoxyflurane (pharmacokinetic studies) or isoflurane (dose-dependency studies) anesthesia and organs were isolated. For pharmacokinetic studies with PTX, time points were 3.5, 7.5, 15, 30, 60, 120, and 240 minutes after dosing. For dose-dependency studies with PTX and MTX, time points of isolation were 30 and 15 minutes after dosing, respectively. Heparinized blood samples were centrifuged at 5,000 rpm for 5 minutes at 4°C and plasma was collected and stored at −20°C until analysis.

Drug analysis
Amounts of PTX in plasma and organs [homogenized in an ice-cold 4% (w/v) bovine serum albumin (BSA) solution using a Polytron homogenizer] were determined using liquid–liquid and solid-phase extraction followed by reversed-phase high-performance liquid chromatography (HPLC) with UV detection, as described before (15). Amounts of MTX and its hydroxylated metabolite, 7OH-MTX, in plasma and organs (homogenized in an ice-cold 4% (w/v) BSA solution) were determined by HPLC analysis as described (16).

Statistical analysis
Statistical evaluation was performed using the 2-sided, unpaired Student’s t test to assess the statistical significance of difference between 2 sets of data. Differences were considered to be statistically significant when P < 0.05.

Results
Role of Oatp1a/1b proteins in PTX pharmacokinetics
To determine the role of Oatp1a/1b transporters in the disposition of PTX in vivo, wild-type and Scoloa/1b−/− mice were dosed with PTX (10 mg/kg intravenous) and drug levels were measured at several time points after administration. The plasma area under the curve (AUC) was 2.2-fold increased in Scoloa/1b−/− mice compared with wild-type mice (1,127 ± 47 min·μg/mL vs. 503 ± 29 min·μg/mL, respectively; P < 0.001; Fig. 1A). Concomitantly, in spite of the higher plasma concentrations, PTX concentrations in the liver were markedly (2-fold) lower in mice lacking Oatp1a/1b transporters (liver AUC was 5,258 ± 209 vs. 10,445 ± 479 min·μg/g for Scoloa/1b−/− and wild-type mice, respectively; P < 0.001; Fig. 1B), illustrating the impact of hepatic Oatp1a/1b transporters on PTX pharmacokinetics. From 7.5 minutes (second time point) after dosing, liver-to-plasma ratios were markedly higher in wild-type compared with Scoloa/1b−/− mice, and they tended to further increase with time (and thus lower plasma PTX concentrations; Fig. 1C). Given the hydrophobic nature of PTX, we had anticipated that there would be a substantial passive diffusion component in its tissue distribution. Indeed, the rather constant liver-to-plasma ratio over time in Scoloa/1b−/− mice suggests that liver uptake of
PTX is predominantly dependent on passive diffusion in absence of Oatp1a/1b transporters. In contrast, the increasing liver-to-plasma ratio over time in the wild-type mice may suggest a relative decrease in passive diffusion, and an increase in Oatp1a/1b contribution to PTX liver distribution with decreasing PTX plasma levels.

Shortly after PTX administration (7.5–15 minutes), more than 40% of the drug had accumulated in the wild-type liver, illustrating the rapid and profound impact of this organ on intravenous PTX pharmacokinetics (Fig. 1B). Interestingly, liver accumulation of PTX in wild-type mice still increased from 3.5 minutes onward (3.5–7.5 minutes, \( P = 0.06 \); 3.5–15 minutes, \( P < 0.05 \)) and only dropped after 15 minutes, whereas in the absence of Oatp1a/1b transporters, PTX concentration in the liver only decreased over this time period. This effect was verified in an independent experiment (data not shown). At the early time point of 3.5 minutes after administration, no significant differences in liver and plasma PTX were observed between wild-type and Slco1a/1b/C0/C0 mice (Fig. 1). Together, these data suggest that at very high plasma concentrations (0–3.5 minutes after dosage; >20 \( \mu \)g/mL), the Oatp1a/1b-mediated liver uptake of PTX is saturated and hepatic PTX uptake is predominantly dependent on other uptake mechanisms, most likely passive diffusion, in both wild-type and Slco1a/1b/C0/C0 mice. Thereafter, Oatp1a/1b transporters start to exert a marked effect on PTX distribution to the liver, even when plasma concentrations are as low as 0.3 \( \mu \)g/mL (Fig. 1).

### Dose-dependent role of Oatp1a/1b transporters in PTX pharmacokinetics

Because of the suggestion of the involvement of saturation processes, wild-type and Slco1a/1b/C0/C0 mice were dosed with 2, 10, or 50 mg/kg of PTX to establish the role of Oatp1a/1b transporters in PTX disposition at different dose levels and plasma concentrations. Tissue and plasma levels of PTX were determined 30 minutes after administration, as at this time point, on the basis of the data in Figure 1, the early distribution phase was over and the impact of Oatp1a/1b on both plasma and liver concentrations was substantial. Plasma levels of PTX were clearly increased in mice lacking Oatp1a/1b transporters compared with wild-type mice at all dosage levels (2.1-, 1.9-, and 1.7-fold increased upon 2, 10, and 50 mg/kg of PTX dosage, respectively; Fig. 2A). Also, the hepatic levels of PTX confirmed a high impact of Oatp1a/1b transporters on PTX distribution over a broad concentration range, as liver accumulation was significantly decreased in Slco1a/1b/C0/C0 mice compared with wild types at all 3 dose levels (1.8-, 2.2-, and 1.5-fold decreased upon 2, 10, and 50 mg/kg of PTX dosage, respectively; Fig. 2B). Although the effect of Oatp1a/1b transporters on plasma and liver levels of PTX after 50 mg/kg of dosage was still marked (1.7- and 1.5-fold, respectively), the fold difference between wild-type and Slco1a/1b/C0/C0 mice was significantly lower than after the dosage of 2 mg/kg of PTX (\( P < 0.05 \) for both plasma and liver levels of PTX). This is compatible with a beginning of
saturation of the Oatp1a/1b-mediated uptake of PTX into the liver at higher plasma concentrations (>20 μg/mL). Higher dosages of PTX were not tolerated by the mice, precluding attempts to fully saturate the Oatp1a/1b uptake component. The white bars shown in Figure 2B correspond to the uptake of PTX into the liver in the absence of Oatp1a/1b transporters. Hypothetically, when PTX is fully dependent on Oatp1a/1b transporters for transporter-mediated uptake into the liver, these white bars represent the remaining passive diffusion-mediated liver uptake of PTX. The part of PTX uptake (% of dose) into the liver mediated by passive diffusion was rather constant at all 3 dosages, as would be expected for a nonsaturable process. In fact, these results suggest that at 2 and 10 mg/kg of dose ~50% of the PTX accumulation in the liver was mediated by active uptake through Oatp1a/1b, and the other ~50% most likely by passive diffusion. At the highest dose (50 mg/kg), however, the Oatp1a/1b-mediated liver uptake of PTX (black bar minus white bar) is clearly decreased (to ~30% of total uptake), suggesting partial saturation of Oatp1a/1b transporters.

We also tested PTX levels in small intestine (including contents) 30 minutes after dosing. These were slightly (albeit not significantly) increased in Slco1a/1b−/− mice dosed with 2 or 50 mg/kg of PTX, but significantly increased in Slco1a/1b−/− mice after 10 mg/kg (Fig. 2C). These results are in line with previous reports that have shown the importance of P-gp- and Mrp2-mediated direct intestinal excretion after intravenous administration of PTX (13, 14). This direct intestinal excretion of PTX is likely dependent on plasma levels of the drug (14), and our results suggest that a presumably decreased biliary excretion of PTX in Slco1a/1b−/− mice (due to the decreased liver PTX levels) is more than offset by an increase in direct intestinal excretion (owing to the increase in plasma PTX levels).

**Dose-dependent role of Oatp1a/1b transporters in MTX pharmacokinetics**

We have previously found that Oatp1a/1b deficiency has a pronounced effect on the pharmacokinetics of MTX at a dose of 10 mg/kg intravenous, with a 4.8-fold increased plasma AUC and 25-fold decreased liver levels of MTX (10). To investigate the effect of Oatp1a/1b transporters on plasma and tissue distribution after much higher doses of MTX, also aiming for a possible saturation effect, we administered 10, 50, and 500 mg/kg of MTX intravenously to wild-type and Slco1a/1b−/− mice. Plasma, liver, and small intestine (including contents) were isolated 15 minutes after administration (clearance of MTX is considerably faster than that of PTX) and MTX levels were determined. Plasma levels of MTX were markedly higher in Slco1a/1b−/− mice compared with wild-type mice at all 3 dose levels (5.8-, 5.7-, and 3.4-fold increased upon 10, 50, and 500 mg/kg of MTX, respectively; Fig. 3A). Liver levels of MTX, on the other hand, were far lower in mice lacking Oatp1a/1b transporters (23.2-, 18.4-, and 30.2-fold decreased upon 10, 50, and 500 mg/kg of MTX dosage, respectively; Fig. 3B). Small intestinal levels of MTX were also substantially decreased in Slco1a/1b−/− mice (10.0-, 18.9-, and 12.9-fold decreased upon 10, 50, and 500 mg/kg of MTX dosage, respectively; Fig. 3B).
12.9-fold decreased for 10, 50, and 500 mg/kg of MTX, respectively; Fig. 3C), most likely reflecting the decreased liver concentrations, resulting in reduced biliary excretion (note that direct excretion of MTX across the intestinal wall is extremely low, even in wild-type mice; refs. 17, 18).

Together, these data show a profound impact of Oatp1a/1b transporters on plasma levels and liver uptake over a wide range of MTX concentrations. Even at the highest practically attainable dose (500 mg/kg), the amount of MTX in the liver of Slco1a/1b−/− mice was only less than 1% of the dose, whereas in wild-type mice this was ~25% (Fig. 3B). In contrast to the PTX data in which we could show a beginning of saturation of Oatp1a/1b-mediated liver uptake of PTX at 50 mg/kg, even at 500 mg/kg of MTX dosage, no significant saturation of Oatp1a/1b transporters was noticed.

The impact of Oatp1a/1b transporters on MTX pharmacokinetics and toxicokinetics was further demonstrated by levels of the main, toxic metabolite of MTX, 7-hydroxy-methotrexate (7OH-MTX). 7OH-MTX is primarily formed in the liver by the oxidation of MTX by aldehyde oxidase 1 and 3 (Aox1 and Aox3; expression of these genes is comparable between wild-type and Slco1a/1b−/− mice; ref. 10). The greatly reduced liver levels of MTX in the Slco1a/1b−/− mice would thus be expected to result in far lower 7OH-MTX levels. Indeed, 7OH-MTX was substantially present in wild-type plasma and liver after administration of 50 and 500 mg/kg of MTX, but undetectable in plasma and below 0.2% of the dose in livers and small intestine (including contents) of Slco1a/1b−/− mice (Fig. 4A–C). The percentage of 7OH-MTX dose in wild-type liver following 500 mg/kg of dosage was markedly lower compared with the amounts of 7OH-MTX after 10 and 50 mg/kg. As this was not the case for parental levels of the drug (Fig. 3B), the availability of MTX to be converted to 7OH-MTX by Aox1 or Aox3 was not the limiting factor. The results may therefore suggest saturation of (one of) these enzymes at 500 mg/kg in wild-type liver.

**Discussion**

Because of the hydrophobic nature of PTX, it is able to pass cell membranes easily by passive diffusion. It is therefore generally thought that uptake transporters, like Oatp1a/1b, have a limited role in in vivo pharmacokinetics of PTX. Yet, results of the present study show that Oatp1a/1b transporters can markedly affect plasma and liver distribution of PTX, and hence its clearance. Results from this study also demonstrate the impact of Oatp1a/1b transporters on liver uptake and systemic exposure of PTX and MTX over a wide range of concentrations. We previously showed an important role of these uptake transporters in fexofenadine pharmacokinetics (10). Together with the results from this study, we have established a marked in vivo impact of Oatp1a/1b transporters on a potentially very broad range of drug substrates, ranging from charged organic anions (MTX) to polar zwitterionic drugs (fexofenadine), and even highly hydrophobic drugs (PTX).
Systemic exposure of PTX was markedly increased (~2-fold) in the absence of Oatp1a/1b transporters, most likely primarily due to the reduced hepatic uptake of the drug (Fig. 1). Interestingly, we show that the effect of Oatp1a/1b transporters on PTX disposition was still marked at low plasma concentrations (Fig. 1A and C), whereas we previously found that at low plasma concentrations (~1 µg/mL), the impact of Oatp1a/1b transporters on MTX disposition became much reduced (10). This is compatible with a relatively high affinity of Oatp1a/1bs for PTX. Also, in line with this high-affinity transport of PTX by Oatp1a/1b transporters on plasma and liver levels of PTX. Again, this is in contrast to our previous observation for MTX disposition, in which the impact of Oatp1a/1b transporters on MTX disposition was immediate, and already 3.5 minutes after intravenous injection of MTX (10 mg/kg), we found markedly increased plasma levels and reduced liver levels in Scl01a1b−/− mice compared with wild-type (10). The most likely explanation for this difference is that, with early high plasma PTX concentrations, initial liver uptake of PTX is dominated by passive diffusion, which is nonsaturable, and that Oatp1a/1b-mediated uptake is saturated. The initial impact of the absence of Oatp1a/1b is therefore low. In contrast, for the anionic MTX, passive diffusion is negligible, and there are apparently no alternative high-capacity, unsaturated liver uptake processes for MTX next to Oatp1a/1b. Because of the apparently very high capacity and K_m of Oatp1a/1bs for PTX, these uptake transporters exert an immediate effect on MTX liver uptake and plasma levels, even at very high plasma concentrations. The beginning saturation of PTX liver uptake (Fig. 2A and B), and the contrasting absence of saturation of MTX liver uptake with higher drug dosages (Fig. 3A and B) further support this interpretation.

Importantly, our results indicate that the role of OATP1A/1B transporters in PTX pharmacokinetics might be clinically relevant, because the peak plasma concentration of PTX in patients after high-dose treatment (275 mg/m²) can vary from about 2 to 11 µg/mL (19). This is well below the concentration in which diffusion is the likely dominant factor for PTX liver uptake and plasma levels. Furthermore, neutropenia is related to plasma concentrations of ~0.08 µg/mL or greater (20, 21). Therefore, OATP1A/1B transporters are most likely not saturated over the clinically relevant range of PTX plasma levels and they might thus markedly contribute to PTX kinetics and/or toxicity. Hence, reduced activity of OATP1A/1B transporters due to polymorphisms or drug–drug interactions might have severe consequences for patients treated with PTX.

The majority of human OATPs have also been detected in certain cancers. OATP1B3, for example, is found in gastric, colon, and pancreatic cancers (22), in breast carcinomas (23), and lung cancer (24). OATP1A2 and OATP2B1 have also been detected in breast tumors (25) and in epithelia of invasive ductal carcinomas of mammary tissue (26), respectively. Given our results, showing a marked in vivo impact of Oatp1a/1b transporters on the pharmacokinetics of PTX and MTX, a possibly important contribution of OATP1A/1B uptake transporters to the cellular sensitivity of tumors to these (and other) anticancer agents should be considered.

When extrapolating our results to the human situation, it should be noted that there are no straightforward orthologs between mouse and human members of the OATP1A/1B transporters. For instance, human OATP1A2 is present in liver cholangiocytes, but not in hepatocytes (27), raising the question raising the question where in the liver the murine Oatp1a proteins are primarily expressed. However, comparison of the impact of the single Scl01b2 knockout (28) with that of the full Scl01a1b knockout (10) on plasma clearance of compounds, such as bilirubin glucuronide, indicates that one or more of the abundant hepatic Oatp1a proteins have a major function in sinusoidal uptake by hepatocytes, analogous to human OATP1B1 and OATP1B3, or mouse Oatp1b2. It therefore seems likely that the Scl01a1b knockout mice give a reasonable impression of the collective functions of the human OATP1A/1B family.

Previous in vitro studies identified human OATP1B3, but not OATP1B1, OATP1A2, or OATP2B1 as a transporter of PTX with a relatively high affinity (K_m ~7 µmol/L, i.e., ~6 µg/mL; refs. 8, 12, 29). This would imply that in humans, OATP1B3 may be the key PTX uptake transporter present at the basolateral membrane. However, one should be careful in extrapolating in vitro results to the in vivo situation. Also, other uptake transporters are present at the basolateral membrane of the liver: for instance, organic anion transporter 2 (OAT2; SLC22A7). Human OAT2, but not its murine ortholog Oat2, was also shown to be a transporter of PTX in vitro, with a K_m value of about 0.15 µmol/L (30,31). Therefore, OATP1B3 might act together with OAT2 in the hepatic uptake of PTX in humans. Clearly, more work will be needed to better sort out the situation in human liver.

In conclusion, Oatp1a/1b transporters play an important role in the disposition of PTX and MTX in vivo across a wide range of (clinically relevant) plasma concentrations, primarily by mediating the hepatic uptake of the drug. These results indicate that variation in OATP1A/1B activity due to genetic variation or drug–drug interactions might affect interindividual variation in anticancer treatment. Moreover, expression of OATP1A/1B transporters in cancer cells might affect tumor penetration and therefore tumor response in patients.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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