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Transporters for Bile Formation in Physiology and Pathophysiology

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Abstract: The liver fulfills many vital functions for the body, among them bile formation and detoxification. Bile salts are organic anions, are the major constituents of bile and are cytotoxic at high concentrations. Detoxification exposes the liver to many harmful compounds. This function is therefore potentially damaging to the liver. Impaired bile formation may lead to hepatic accumulation of bile salts and subsequently to liver disease. Diagnosis of liver diseases involves the measurement of so-called liver function parameters. This overview aims to characterize and summarize the role of organic anion transporters in bile formation at the protein level under normal physiologic conditions and in liver function tests used for diagnosing liver diseases in pathophysiologic situations.

Keywords: Function test · Liver · Pathophysiology · Physiology · Transporter

Bruno Stieger was trained as a biochemist at the Federal Institute of Technology in Zurich Switzerland and holds a PhD in biochemistry from the same institution. After postdoctoral fellowships at the Biozentrum of the University Basel and at the Johns Hopkins University School of Medicine in Baltimore (USA) he joined in 1988 the Department of Clinical Pharmacology and Toxicology of the University Hospital Zurich. His research interests are physiology and pathophysiology of bile formation, drug transport and interaction of drugs with the liver. He was the recipient of the Adolf Windaus Award in 2018.

Introduction

The liver has a strategic location within the circulatory system. Blood from the intestine flowing back to the systemic circulation reaches first the liver. Hence, the liver is – after the intestine – the first organ exposed to intestinally absorbed nutrients and foreign compounds. Due to this location, the liver is also a second barrier behind the intestinal wall for preventing the entry of harmful substances into the body *via* the oral route.[1,2] This barrier function may be impaired to variable extents in disease states,[3,4] which in turn will lead to variable liver exposure by gut-entering substances. Therefore, the liver is always at risk of insults by xenobiotics, toxins or pathogens, which manage to cross the intestinal barrier.[1] Additional key functions of the liver such as metabolism and energy homeostasis, protein synthesis and secretion, detoxification or bile formation also affect the entire body.[5]

Bile Formation

Bile acids (BA) are divided into primary and secondary BAs. The latter are formed by the gut microbiome in the intestine.[6] The major constituents of bile are bile salts (BS), organic anions such as conjugates of bilirubin and lipids.[7] BSs and unconjugated primary and secondary BAs produced by the gut flora are absorbed from the portal blood into hepatocytes. Within hepatocytes the BAs, additionally also originating from *de novo* synthesis, are rapidly conjugated to become BSs. These are, together with BSs absorbed from the portal blood, secreted across the canalicular liver plasma membrane (cLPM) and drained *via* the gall bladder into the small intestine. In the intestine, BSs are almost quantitatively absorbed and shipped back into the liver *via* the portal vein, where their journey starts again. This process is termed enterohepatic circulation.[8] The transport systems involved in hepatocellular handling of BAs and BSs are cloned and functionally well characterized.[9,10] These transporters include for the uptake from the blood plasma the Na^+-taurocholate-cotransporting polypeptide (NTCP) and the organic anion transporting polypeptides (OATPs) OATP1B1, OATP1B3, and OATP2B1. Export of BSs from hepatocytes into bile against a steep concentration gradient is mediated by the bile salt export pump (BSEP), an ATP-binding cassette (ABC) transporter. Under pathologic conditions with elevation of intracellular BS and BA levels in hepatocytes, multidrug resistance-associated proteins (MRPs) MRP3, MRP4, and the heterodimeric organic solute transporter OSTα/OSTβ, all expressed at the basolateral membrane, may act as salvage transporters for BSs.[11,12]

BS export into the canaliculus by BSEP constitutes the rate-limiting step of trans-hepatocellular BS flux. Therefore, BSEP is the key transporter driving the enterohepatic circulation of BSs and for keeping intracellular BSs low. The substrate specificity of BSEP is restricted with very few exceptions to BSs.[9] In addition, MRP2 acts as a canalicular efflux system for glucuronidated secondary BSs,[12] while sulfated secondary BSs are substrates of ABCG2.[13] Similarly, the main substrates for NTCP are BSs, but it can transport additional substrates, such as drugs.[14] In addition to contributing to BA uptake into hepatocytes, OATPs have a broad substrate specificity and are key transporters for hepatocellular drug uptake.[15]

Interplay of Bile Salt Transporters with Membranes

The intracanalicular BS concentration is very high.[16] It cannot be directly determined, but may exceed 50 mM in humans,[17] which is above the critical micellar concentration of BSs.[18] BSs have detergent properties[19] and may damage cells from the inside and/or outside.[20] BSs can solubilize *in vitro* isolated cLPM[21,22] and *in vivo* affect the maximal BS secretory rate due to their detergent properties.[23] The cLPM contains detergent-resistant microdomains (so-called rafts),[24] which are enriched in sphingomyelin and cholesterol.[25] It was also demonstrated that incubating isolated cLPM vesicles with BSs leads to the formation of microdomains.[18] These microdomains containing ABC-transporters like BSEP[18,24] protect the cLPM against the detergent action of

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intracanalicular BSs. The transport activity of ABC transporters such as BSEP and MRP2 is modulated by the membrane cholesterol content[26–28] and structural analysis of ABC-transporters revealed tightly bound cholesterol and phospholipid molecules.[29] As increased BS secretion leads to increased biliary cholesterol secretion,[30] the cholesterol content of cLPM may be lowered in situations of high BS output and consequently lower indirectly the activity of canalicular ABC transporters as a protective mechanism against excessive loss of lipids from the cLPM. In addition, partitioning in and out of cholesterol-rich microdomains may also be a passive regulatory mechanism of canalicular ABC transporter capacity.

Impaired Liver Function

Liver diseases are an important clinical entity and are, for example in Europe, the second leading cause for loss of years of working life.[31] Liver diseases are inherited or acquired and many impair bile formation, which in turn may lead to intracellular accumulation of BSs in hepatocytes, a process termed cholestasis. Elevated intracellular BSs are cytotoxic to hepatocytes and other cells.[20] Intracellular BSs may *e.g.* impair mitochondrial function[32] or lead to endoplasmic reticulum stress.[33,34] Impaired BSEP activity, if persistent, may lead to cholestatic liver disease,[35,36] since BSEP is the key transporter exporting BSs from hepatocytes. In addition to inherited defective canalicular exporter functions, inherited defects in the biosynthesis of BAs[37] or disfunctions of the tight junctions[38] sealing canalicular bile from the space of Disse can lead to overt liver disease. Acquired forms of cholestasis have many causes. Drugs inhibiting BSEP[39,40] or MDR3[41–43] may lead to prototypical forms of acquired cholestatic liver disease. It is important to realize that drug-induced liver injury encompasses many different pathogenic mechanisms in addition to transporter inhibition.[44] In susceptible women, pregnancy may lead to intrahepatic cholestasis of pregnancy, another prototypical form of acquired liver disease, which may involve transport systems.[45] In contrast to the above-mentioned examples, viral hepatitis, liver disease as a consequence of alcohol abuse, obesity or life-style induced liver disease are by far more prevalent.[31]

While currently the clinical focus is often on advanced forms of liver disease, diagnosis and management of early forms of liver disease are frequently not considered in practice.[31] Hence, early detection of impaired liver function is important. Elevated liver values are detected in many cases incidentally in primary care and are associated with an increase in mortality as well as comorbidities.[46] Hence, there is a need for specific as well as technically unsophisticated liver function tests (LFTs) to improve this situation. Measurements of so-called liver parameters are an important part of diagnosing liver disease. These parameters often only allow indirect conclusions on liver function. For example, serum bilirubin levels give indirect information on the uptake, metabolic, and excretory/secretory functions of the liver.[47] This needs to be judged against hemolysis leading also to elevated bilirubin levels.

Clinical Monitoring of Liver Function

In principle, LFTs can be divided into passive LFTs, including determination of liver enzymes as well as clinical grading systems, and dynamic functional LFTs such as clearance measurements of dyes, *e.g.* indocyanine green (ICG)[48] or other molecules cleared by the liver or metabolic tests assessing the functional capacity of the liver.[47,49] Such tests are not only used for diagnostic purposes but also in a prognostic manner for the management of patients with (severe) liver disease.[47,50] Dynamic LFTs determine clearances and are now also developed for directly measuring with imaging technologies the handling of substances by the liver, *e.g.* magnetic resonance imaging (MRI) or single photon emission tomography (SPECT).[51,52] The finding, for instance, that scintigraphic *in vivo* determination of liver function by monitoring the hepatobiliary transport of ^{99m}Tc-mebrofenin improves the postoperative outcome of the risk assessment for patients needing major liver resection[53,54] highlights the clinical relevance of this approach. It is well established that liver disease leads to altered expression of hepatocellular transporters,[55] which in turn likely influences the outcome of LFTs performed with imaging or by clearance determination. Therefore, *in vitro* identification of hepatocellular transporters involved in handling of liver imaging agents is highly warranted. This is a research area being currently actively pursued.[56,57] SPECT and positron emission tomography (PET) imaging compounds applied to humans and tested *in vitro* with organic anion transporters in heterologous expression systems are listed in Table 1.

MRI agents are highly membrane impermeable. Gd-EOB-DTPA was found *in vitro* to be a substrate for NTCP, OATP1B1 and OATP1B3, but not for OATP2B1.[58] Investigation of efflux systems revealed MRP2 and MRP3 as Gd-EOB-DTPA transporters.[59] Gd-BOPTA is *in vitro* a substrate for OATP1B1.[60] A typical serum parameter in static LFTs is the determination of bilirubin measured in conjunction with transaminases. It is important to keep in mind that hepatocellular uptake of bilirubin is mediated by the two transport systems OATP1B1 and OATP1B3[61] and defects in these transporters lead to hyperbilirubinemia.[62] Hence, strictly speaking, bilirubin could also be considered as a dynamic liver function marker. In addition, variants or genetic defects in these transporters will affect the outcome of MRI imaging with contrast agents transported by these two OATPs as demonstrated for OATP1B1, for example.[63]

Imaging techniques utilizing ultrasound, computed tomography or MRI give in addition to functional assessment of the liver also information on morphological aspects of the entire hepatobiliary system[64] and help diagnose benign or malignant liver lesions.[65] Contrast agents may, depending on the time point of imaging after application accumulate or be lost in lesions resulting in hyper- or hypointense signals relative to the surrounding healthy tissue. In general, hepatic imaging can be divided into three distinct phases: the arterial phase, the portal venous phase, and the delayed venous phase.[66] As outlined above, contrast agents do not freely penetrate cell membranes. Therefore they need the expression of transporters mediating uptake into or export of imaging agents from lesions.[51,67–71] The expression of these transporters has a strong impact on imaging results of focal liver diseases.[69,72] In addition to MRI agents, the PET imaging agent [^{18}F]fluoromethylcholine also shows a promising potential for the identification and classification of focal liver lesions.[73]

The liver handles a large amount of bile salts each day by extracting them from the portal blood plasma and secreting them into the biliary tree. It is known for quite some time that BSs are elevated in the plasma in patients with liver disease[74] and it was later demonstrated *in vivo* that in patients with liver disease the clearance of glycocholate is reduced[75] and that the *in vivo* clearances of taurocholate and ICG correlate well.[48] However, because of the endogenous BS pool present in humans, clearance measurements require radioactively labelled BSs[75] and application of such BSs may not be the first method of choice. As an alternative with short-lived isotopes, BS transport *in vivo* is currently explored by PET, wherein hepatic transport of a BA derivative can be monitored in healthy individuals and patients.[76,77] Such techniques expose patients to internal radiation and require complex methodologies. An alternate method is using fluorescently labelled or intrinsically fluorescent compounds. Given that many BS transport systems are well characterized, fluorescently labelled BAs or BSs seem attractive markers for liver function. In support of this concept, a pilot study showed that the plasma clearance of the fluorescent BS cholyl-L-lysyl-fluorescein is reduced in patients with liver cirrhosis in comparison to healthy

Table 1. PET substrates tested on hepatocellular organic anion transporters. Data are from individual transporters expressed heterologously in different cell lines; NT not transported. Inhibitor: Radioactively labelled taurocholate was used as substrate.

	NTCP	OATP1B1	OATP1B3	OATP2B1	BSEP	MRP2	MRP3	MRP4	ABCG2	Ref.
[^{11}C]erlotinib		NT	NT	substrate						[107]
3α-[^{18}F]fluorocholic acid	inhibitor	inhibitor			inhibitor					[108]
3β-[^{18}F] fluorochenodeoxy-cholic acid	inhibitor	inhibitor			inhibitor					[108]
3β-[^{18}F] fluoroglycocholic acid	inhibitor	inhibitor			inhibitor					[108]
2β-[^{18}F]fluorocholic acid	inhibitor	inhibitor			inhibitor					[108]
7β-[^{18}F]fluorocholic acid	inhibitor	inhibitor			inhibitor					[108]
[^{18}F]pitavastatin derivative ([^{18}F]PTV-F1)		substrate	substrate							[109]
[^{11}C]tariquidar		NT	NT	NT						[110]
[^{11}C]-SC-62807		substrate	substrate						substrate	[111]
CA-lys-[^{18}F]TFA (cholate derivative)	substrate									[112]
LCA[^{18}F]TD (lithocholate derivative)	substrate	substrate	substrate		substrate					[113]
[^{99m}]Tc-mebrofenin	NT	substrate	substrate	NT		substrate	substrate			[81,114–116]
[^{99m}]Tc-N-pyridoxyl-5-methyl-tryptophan		substrate	substrate	NT		substrate				[117]
[^{99m}Tc]-DTPA-CDCA (chenodeoxycholate derivative)		substrate	substrate			substrate				[116]
[^{99m}Tc]-DTPA-CA (cholate derivative)		substrate	substrate			substrate				[116]
[^{131}I]6-β-iodomethyl-19-norcholesterol	NT	substrate	substrate	NT	NT	NT	NT	NT	substrate	[118]
[99mTc] mercaptoacetyltri-glycine						substrate		substrate	NT	[119]
[^{123}I]MIBG (m-iodo-benzyl-guanidine)	NT	NT	NT	NT				substrate		[120]

controls.[78] It was later found that this BS derivative is neither a substrate of NTCP nor of BSEP.[79] Hence, such novel BS derivatives require after synthesis a careful *in vitro* characterization with respect to transporter specificity prior to *in vivo* application in humans. Introduction of fluorophores into BSs and their assessment *in vitro* as potential substrates of BS and BA transporters has been reported several times and data are listed in Table 2.

Spectrophotometric determination of ICG clearance is routinely used to assess liver function[50] and can also be performed transcutaneously, thus allowing continuous monitoring of plasma levels of ICG and therefore also liver function.[80] The transport systems mediating hepatocellular uptake of ICG are known.[81] Additionally, the fluorophore fluorescein (and potentially others) used for labelling BSs is a good substrate for many OATPs.[82–84] This highlights the necessity for highly pure preparations of fluorescently labelled BSs, if they are intended for monitoring liver function *in vivo* or in cells expressing several organic anion transporters.[85] Table 3 lists various dyes tested *in vitro* as substrates for hepatocellular organic anion transporters.

Currently, exogenous markers for drug transporters are often used by a microdosing approach.[86–88] Surrogate endogenous biomarkers for transport systems, such as for drugs, are a valid alternative for transport studies with drugs. For example, coproporphyrin-I and coproporphyrin-III are substrates for OATP1B1 and OATP1B3.[89,90] Hepatocellular efflux of coproporphyrin I is mediated by MRP2.[91] Endogenous transporter biomarkers are currently actively searched for and characterized in humans including clinical studies with drugs.[92–96]

Table 2. Fluorescent BA derivatives tested on hepatocellular organic anion transporters. Data are from individual transporters expressed heterologously in different cell lines; NT not transported.

	NTCP	OATP1B1	OATP1B3	OATP2B1	BSEP	MRP2	MRP3	ABCG2	Ref.
chenodeoxycholic acid 7-nitrobenz-2-oxa-1,3-diazole (CDCA-NBD)		substrate	substrate						[121,122]
N-(24-[7-(4-N,N-dimethylaminosulfonyl-2,1,3-benzoxadiazole)]amino-3a,7a,12a-trihydroxy-27-nor-5b-cholestan-26-oyl)-2'-aminoethanesulfonate (tauro-nor-THCA-24-DBD)					substrate				[123]
N-(24-[7-(4-N,N-dimethylaminosulfonyl-2,1,3-benzoxadiazole)]amino-3α,7α,12α-trihydroxy-27-nor-5β-cholestan-26-oyl)-2'-aminoethanesulfonate (tauro-nor-THCA-24-DBD)	substrate	substrate	substrate						[124]
cholylglycylamidofluorescein (CGamF)		substrate	substrate						[125]
cholylglycylamidofluorescein (CGamF)	substrate				substrate				[126]
chenodeoxycholylglycylamido-fluorescein (CDCGamF)	substrate				substrate				[126]
cholyl-L-lysyl-fluorescein (CLF)	NT	substrate	substrate	NT	NT	substrate	substrate	NT	[79]
cholic acid-en-nitrobenzofurazan	NT	substrate	NT	substrate	NT	NT			[85]
cholic acid-en-dansyl	substrate	NT	substrate	substrate	NT	NT			[85]
cholic acid-en-pacific blue	NT	substrate	substrate	NT	substrate	NT			[85]
chenodeoxycholic acid-en-nitrobenzofurazan	NT	substrate	substrate	substrate	NT	NT			[85]
chenodeoxycholic acid-en-dansyl	NT	NT	substrate	substrate	NT	NT			[85]
chenodeoxycholic acid-en-pacific blue	Nt	NT	substrate	substrate	substrate	substrate			[85]

Outlook

While the role of transporters in LFTs is now well established and generally accepted, several issues remain. First, as many transporters have overlapping substrate specificities, the *in vivo* contribution of individual transporters to results is difficult to elucidate at best. Second, driving forces have not been worked out in detail for all transporters. For example, the driving force of OATPs is not yet clearly worked out, but it most likely involves organic anion exchangers, where bicarbonate in the liver may be a likely counterion.[97] Different physiologic and pathophysiologic states may, however, modify driving forces for transporters and therefore also affect the outcomes of LFTs based on transport. Third, a considerable interindividual variability of transporter protein expression levels exists in healthy individuals. Examples of the span of protein expression levels for selected hepatocellular transporters are given in Table 4. Fourth, transporters in humans are often polymorphic and different variants may have different transport properties as well as protein expression levels.[98–101] These properties have been demonstrated to have an impact on drug disposition,[102] adverse drug actions[103] or MRI imaging, for example.[104]

In conclusion, biological membranes are a primordial component of life, as they allow building of units of life and sealing them tightly from the intracellular or extracellular environment.[105] Exchange of substances across biological membranes therefore necessitates transport proteins embedded in biological barriers. Today, the biological significance of transporters is generally accepted. In liver, hepatocellular transporters are now well established to be relevant for understanding molecular mechanisms of LFTs as well as liver imaging. In future, more work is needed for defining the driving forces as well as their alterations in pathophysiologic situations. This will certainly help increase the predictive power of LFTs as well as develop better pharmacokinetic models for drug disposition. Finally, LFTs for *in vivo* monitoring of biochemical reactions producing harmful metabolites may in the future complement the arsenal of tests based on transport systems.[106]

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[1] A. Corsini, M. Bortolini, *J. Clin. Pharmacol*. **2013**, *53*, 463, https://doi.org/10.1002/jcph.23.
[2] N. Selvapatt, A. Singanayagam, J. Wendon, C. G. Antoniades, *Intensive Care Med*. **2014**, *40*, 1363, https://doi.org/10.1007/s00134-014-3349-x.
[3] K. R. Groschwitz, S. P. Hogan, *J. Allergy Clin. Immunol.* **2009**, *124*, 3, https://doi.org/10.1016/j.jaci.2009.05.038.
[4] D. Ramanan, K. Cadwell, *Cell Host Microbe* **2016**, *19*, 434, https://doi.org/10.1016/j.chom.2016.03.003.
[5] J. K. Corless, H. M. Middleton, 3rd, *Arch. Intern. Med.* **1983**, *143*, 2291, https://doi.org/10.1001/archinte.143.12.2291.

Table 3. Dyes tested on hepatocellular organic anion transporters. Data are from individual transporters expressed heterologously in different cell lines; NT not transported.

	NTCP	OATP1B1	OATP1B3	OATP2B1	MRP2	ABCG2	Ref.
fluorescein		substrate	substrate	NT			[82,127]
fluorescein		substrate	substrate	substrate			[83,83]
fluorescein-methotrexate		substrate	substrate	substrate			[83,128]
pyranine		substrate	substrate	substrate	substrate	NT	[128]
cascade blue hydrazide		substrate	substrate	substrate	substrate	substrate	[128,129]
sulforhodamine 101		substrate			substrate	NT	[128]
live/dead violet					NT	substrate	[128]
live/dead green		substrate	substrate	substrate	substrate	NT	[128,129]
lucifer yellow						substrate	[128]
zombie violet		substrate	substrate	substrate	substrate	NT	[128,129]
Alexa Fluor 405		substrate	substrate	substrate			[129]
dibromofluorescein		substrate	substrate	substrate			[84]
Oregon Green		substrate	substrate	substrate			[84]
Fluo-3		substrate		substrate	substrate		[84,130,131]
8-fluorescein-cAMP		substrate	substrate	substrate			[84,132]
dichlorofluorescein			substrate				[84]
Oregon Green 488 taxol		substrate	substrate				[127]
Alexa Fluor 488 methotrexate		NT	NT				[127]
indocyanine green	substrate	NT	substrate	NT			[81]
indocyanine green		substrate	substrate				[60]
5(6)-carboxy-2,′7′-dichlorofluorescein					substrate		[133]

[6] D. V. Guzior, R. A. Quinn, *Microbiome* **2021**, *9*, 140, https://doi.org/10.1186/s40168-021-01101-1.
[7] A. Esteller, *World J. Gastroenterol*. **2008**, *14*, 5641, https://doi.org/10.3748/wjg.14.5641.
[8] P. A. Dawson, T. Lan, A. Rao, *J. Lipid Res.* **2009**, *50*, 2340, https://doi.org/R900012-JLR200 10.1194/jlr.R900012-JLR200.
[9] B. Stieger, *Handb. Exp. Pharmacol*. **2011**, *201*, 205, https://doi.org/10.1007/978-3-642-14541-4_5.
[10] M. J. Pollheimer, P. Fickert, B. Stieger, *Mol. Aspects Med.* **2014**, *37*, 35, https://doi.org/S0098-2997(13)00075-7 10.1016/j.mam.2013.10.001.
[11] A. D. Rodrigues, Y. Lai, M. E. Cvijic, L. L. Elkin, T. Zvyaga, M. G. Soars, *Drug Metab. Dispos*. **2014**, *42*, 566, https://doi.org/10.1124/dmd.113.054205.
[12] E. Halilbasic, T. Claudel, M. Trauner, *J. Hepatol*. **2013**, *58*, 155, https://doi.org/10.1016/j.jhep.2012.08.002.
[13] A. G. Blazquez, O. Briz, M. R. Romero, R. Rosales, M. J. Monte, J. Vaquero, R. I. Macias, D. Cassio, J. J. Marin, *Mol. Pharmacol*. **2012**, *81*, 273, https://doi.org/10.1124/mol.111.075143.
[14] M. S. Anwer, B. Stieger, *Pflugers Arch*. **2014**, *466*, 77, https://doi.org/10.1007/s00424-013-1367-0.
[15] B. Hagenbuch, B. Stieger, *Mol. Aspects Med*. **2013**, *34*, 396, https://doi.org/10.1016/j.mam.2012.10.009S0098-2997(12)00123-9
[16] J. L. Boyer, *Comprehensive Physiology* **2013**, *3*, 1035, https://doi.org/10.1002/cphy.c120027.
[17] M. C. Carey, D. M. Small, *J. Clin. Invest*. **1978**, *61*, 998, https://doi.org/10.1172/JCI109025.
[18] C. Guyot, B. Stieger, *J. Hepatol*. **2011**, *55*, 1368, https://doi.org/S0168-8278(11)00375-8 10.1016/j.jhep.2011.04.014.
[19] A. F. Hofmann, D. M. Small, *Annu. Rev. Med.* **1967**, *18*, 333, https://doi.org/10.1146/annurev.me.18.020167.002001.
[20] A. F. Hofmann, *Arch. Intern. Med*. **1999**, *159*, 2647, https://doi.org/10.1001/archinte.159.22.2647.
[21] I. M. Yousef, M. M. Fisher, *Can. J. Biochem*. **1976**, *54*, 1040.
[22] T. Gerloff, P. J. Meier, B. Stieger, *Liver* **1998**, *18*, 306, https://doi.org/10.1111/j.1600-0676.1998.tb00810.x.
[23] I. M. Yousef, S. Barnwell, F. Gratton, B. Tuchweber, A. Weber, C. C. Roy, *Am. J. Physiol*. **1987**, *252*, G84, https://doi.org/10.1152/ajpgi.1987.252.1.G84.
[24] M. G. Ismair, S. Hausler, C. A. Stuermer, C. Guyot, P. J. Meier, J. Roth, B. Stieger, *Hepatology* **2009**, *49*, 1673, https://doi.org/10.1002/hep.22807.
[25] K. J. van Erpecum, M. C. Carey, *Biochim. Biophys. Acta* **1997**, *1345*, 269.
[26] A. Telbisz, M. Muller, C. Ozvegy-Laczka, L. Homolya, L. Szente, A. Varadi, B. Sarkadi, *Biochim. Biophys. Acta* **2007**, *1768*, 2698, https://doi.org/S0005-2736(07)00243-X 10.1016/j.bbamem.2007.06.026.

Table 4. Protein expression spans of hepatocellular organic anion transporters. The expression span is given as the ratio between highest and lowest amount of transporter published.

	NTCP	OATP1B1	OATP1B3	OATP2B1	BSEP	MRP2	MRP3	ABCG2	Ref.
Western blotting					20	262			[98]
Western blotting						7		3	[134]
Western blotting		70	48						[99]
proteomics	3		3		4				[135]
proteomics						7			[136]
proteomics								4	[137]
proteomics		7	8	5					[100]
proteomics	3	7			3	6	4		[138]
proteomics		7	31	10					[101]
proteomics	8	6	4	2	4	2	2	4	[139]
proteomics		6	4	6	3	5	4		[140]
proteomics		8	27	20	30	7	49		[141]
proteomics		7	6	5	3	4	7		[142]
proteomics	57	6	6	2					[143]
proteomics		13	7	10	4	4	5		[144]

[27] E. Kis, E. Ioja, T. Nagy, L. Szente, K. Heredi-Szabo, P. Krajcsi, *Drug Metab. Dispos*. **2009**, *37*, 1878, https://doi.org/dmd.108.024778 10.1124/dmd.108.024778.

[28] C. Guyot, L. Hofstetter, B. Stieger, *Mol. Pharmacol*. **2014**, *85*, 909, https://doi.org/10.1124/mol.114.092262.

[29] B. Stieger, J. Steiger, K. P. Locher, *Biochim. Biophys. Acta Mol. Basis Dis*. **2021**, *1867*, 166079, https://doi.org/10.1016/j.bbadis.2021.166079.

[30] A. Dikkers, U. J. Tietge, *World J. Gastroenterol*. **2010**, *16*, 5936, https://doi.org/10.3748/wjg.v16.i47.5936.

[31] T. H. Karlsen, N. Sheron, S. Zelber-Sagi, P. Carrieri, G. Dusheiko, E. Bugianesi, R. Pryke, S. J. Hutchinson, B. Sangro, N. K. Martin, M. Cecchini, M. A. Dirac, A. Belloni, M. Serra-Burriel, C. Y. Ponsioen, B. Sheena, A. Lerouge, M. Devaux, N. Scott, M. Hellard, H. J. Verkade, E. Sturm, G. Marchesini, H. Yki-Jarvinen, C. D. Byrne, G. Targher, A. Tur-Sinai, D. Barrett, M. Ninburg, T. Reic, A. Taylor, T. Rhodes, C. Treloar, C. Petersen, C. Schramm, R. Flisiak, M. Y. Simonova, A. Pares, P. Johnson, A. Cucchetti, I. Graupera, C. Lionis, E. Pose, N. Fabrellas, A. T. Ma, J. M. Mendive, V. Mazzaferro, H. Rutter, H. Cortez-Pinto, D. Kelly, R. Burton, J. V. Lazarus, P. Gines, M. Buti, P. N. Newsome, P. Burra, M. P. Manns, *Lancet* **2022**, *399*, 61, https://doi.org/10.1016/S0140-6736(21)01701-3.

[32] S. Krahenbuhl, C. Talos, S. Fischer, J. Reichen, *Hepatology* **1994**, *19*, 471, https://doi.org/10.1002/hep.1840190228.

[33] T. Adachi, T. Kaminaga, H. Yasuda, T. Kamiya, H. Hara, *J. Clin. Biochem. Nutr*. **2014**, *54*, 129, https://doi.org/10.3164/jcbn.13-46.

[34] K. Wang, *Cell Death Dis*. **2014**, *5*, e996, https://doi.org/10.1038/cddis.2013.499.

[35] G. P. Aithal, P. B. Watkins, R. J. Andrade, D. Larrey, M. Molokhia, H. Takikawa, C. M. Hunt, R. A. Wilke, M. Avigan, N. Kaplowitz, E. Bjornsson, A. K. Daly, *Clin. Pharmacol. Ther*. **2011**, *89*, 806, https://doi.org/clpt201158 10.1038/clpt.2011.58.

[36] L. N. Bull, R. J. Thompson, *Clin. Liver Dis.* **2018**, *22*, 657, https://doi.org/10.1016/j.cld.2018.06.003.

[37] P. T. Clayton, *J. Inherit. Metab. Dis*. **2011**, *34*, 593, https://doi.org/10.1007/s10545-010-9259-3.

[38] S. Amirneni, N. Haep, M. A. Gad, A. Soto-Gutierrez, J. E. Squires, R. M. Florentino, *World J. Gastroenterol*. **2020**, *26*, 7470, https://doi.org/10.3748/wjg.v26.i47.7470.

[39] B. Stieger, *Drug Metab. Rev*. **2010**, *42*, 437, https://doi.org/10.3109/03602530903492004.

[40] R. E. Morgan, C. J. van Staden, Y. Chen, N. Kalyanaraman, J. Kalanzi, R. T. Dunn, 2nd, C. A. Afshari, H. K. Hamadeh, *Toxicol. Sci*. **2013**, *136*, 216, https://doi.org/10.1093/toxsci/kft176.

[41] K. He, L. Cai, Q. Shi, H. Liu, T. F. Woolf, *Chem. Res. Toxicol*. **2015**, *28*, 1987, https://doi.org/10.1021/acs.chemrestox.5b00201.

[42] Z. M. Mahdi, U. Synal-Hermanns, A. Yoker, K. P. Locher, B. Stieger, *Mol. Pharmacol*. **2016**, *90*, 23, https://doi.org/10.1124/mol.116.103390.

[43] M. D. Aleo, F. Shah, K. He, P. D. Bonin, A. D. Rodrigues, *Chem. Res. Toxicol.* **2017**, *30*, 1219, https://doi.org/10.1021/acs.chemrestox.7b00048.

[44] R. J. Andrade, N. Chalasani, E. S. Bjornsson, A. Suzuki, G. A. Kullak-Ublick, P. B. Watkins, H. Devarbhavi, M. Merz, M. I. Lucena, N. Kaplowitz, G. P. Aithal, *Nat. Rev. Dis. Primers*. **2019**, *5*, 58, https://doi.org/10.1038/s41572-019-0105-0.

[45] N. A. Terrault, C. Williamson, *Gastroenterology* **2022**, https://doi.org/10.1053/j.gastro.2022.01.060.

[46] J. Wangler, M. Jansky, *BMC Prim. Care* **2022**, *23*, 104, https://doi.org/10.1186/s12875-022-01714-x.

[47] L. T. Hoekstra, W. De Graaf, G. A. A. Nibourg, M. Heger, R. J. Bennink, B. Stieger, T. M. van Gulik, *Ann. Surg.* **2013**, *257*, 27, https://doi.org/10.1097/SLA.0b013e31825d5d47.

[48] G. Paumgartner, *Schweiz Med. Wochenschr*. **1975**, 105, 1.

[49] R. T. Stravitz, Y. Ilan, *Liver Int*. **2017**, *37*, 328, https://doi.org/10.1111/liv.13268.

[50] B. Stieger, M. Heger, W. de Graaf, G. Paumgartner, T. van Gulik, *Eur. J. Pharmacol*. **2012**, *675*, 1, https://doi.org/S0014-2999(11)01515-9 10.1016/j.ejphar.2011.11.048.

[51] C. M. Pastor, B. Mullhaupt, B. Stieger, *Drug Metab. Dispos*. **2014**, *42*, 675, https://doi.org/dmd.113.055707 10.1124/dmd.113.055707.

[52] F. Rassam, P. B. Olthof, R. J. Bennink, T. M. van Gulik, *Visc. Med*. **2017**, *33*, 442, https://doi.org/10.1159/000480385.

[53] K. P. Cieslak, R. J. Bennink, W. de Graaf, K. P. van Lienden, M. G. Besselink, O. R. Busch, D. J. Gouma, T. M. van Gulik, *HPB (Oxford)* **2016**, *18*, 773, https://doi.org/10.1016/j.hpb.2016.06.006.

[54] F. Rassam, P. B. Olthof, H. Richardson, T. M. van Gulik, R. J. Bennink, *Nucl. Med. Commun*. **2019**, *40*, 297, https://doi.org/10.1097/MNM.0000000000000973.

[55] N. Thakkar, J. R. Slizgi, K. L. R. Brouwer, *J. Pharm. Sci.* **2017**, *106*, 2282, https://doi.org/10.1016/j.xphs.2017.04.053.

[56] A. Mann, I. Semenenko, M. Meir, S. Eyal, *AAPS J*. **2015**, *17*, 788, https://doi.org/10.1208/s12248-015-9752-6.

[57] A. Testa, M. Zanda, C. S. Elmore, P. Sharma, *Mol. Pharm*. **2015**, *12*, 2203, https://doi.org/10.1021/acs.molpharmaceut.5b00059.

[58] M. Leonhardt, M. Keiser, S. Oswald, J. Kuhn, J. Jia, M. Grube, H. K. Kroemer, W. Siegmund, W. Weitschies, *Drug. Metab. Dispos*. **2010**, *38*, 1024, https://doi.org/dmd.110.032862 10.1124/dmd.110.032862.

[59] J. Jia, D. Puls, S. Oswald, G. Jedlitschky, J. P. Kuhn, W. Weitschies, N. Hosten, W. Siegmund, M. Keiser, *Invest. Radiol*. **2014**, *49*, 78, https://doi.org/10.1097/RLI.0b013e3182a70043.

[60] Y. H. Lee, M. R. Wu, J. K. Hsiao, *Int. J. Mol. Sci*. **2021**, *22*, https://doi.org/10.3390/ijms22168797.

[61] P. Tatrai, P. Krajcsi, *Pharmaceutics* **2020**, *12*, https://doi.org/10.3390/pharmaceutics12080755.

[62] D. Keppler, *Drug. Metab. Dispos*. **2014**, *42*, 561, https://doi.org/10.1124/dmd.113.055772.

[63] A. Nassif, J. Jia, M. Keiser, S. Oswald, C. Modess, S. Nagel, W. Weitschies, N. Hosten, W. Siegmund, J. P. Kuhn, *Radiology* **2012**, *264*, 741, https://doi.org/10.1148/radiol.12112061.

[64] T. Duan, H. Y. Jiang, W. W. Ling, B. Song, *World J. Gastroenterol*. **2022**, *28*, 1625, https://doi.org/10.3748/wjg.v28.i16.1625.

[65] E. K. O'Neill, J. R. Cogley, F. H. Miller, *Clin. Liver Dis*. **2015**, *19*, 99, https://doi.org/10.1016/j.cld.2014.09.006.

[66] S. Maniam, J. Szklaruk, *World J. Radiol*. **2010**, *2*, 309, https://doi.org/10.4329/wjr.v2.i8.309.

[67] B. E. Van Beers, J. L. Daire, P. Garteiser, *J. Hepatol.* **2015**, *62*, 690, https://doi.org/10.1016/j.jhep.2014.10.014.

[68] B. E. Van Beers, P. Garteiser, B. Leporq, P. E. Rautou, D. Valla, *Semin. Liver Dis.* **2017**, *37*, 243, https://doi.org/10.1055/s-0037-1603651.

[69] A. Kitao, O. Matsui, N. Yoneda, K. Kozaka, S. Kobayashi, W. Koda, D. Inoue, T. Ogi, K. Yoshida, T. Gabata, *Eur. Radiol*. **2020**, *30*, 3438, https://doi.org/10.1007/s00330-020-06687-y.

[70] S. Poetter-Lang, N. Bastati, A. Messner, A. Kristic, A. Herold, J. C. Hodge, A. Ba-Ssalamah, *Abdom. Radiol. (NY)* **2020**, *45*, 3532, https://doi.org/10.1007/s00261-020-02779-x.

[71] M. Ronot, B. Leporq, B. E. Van Beers, V. Vilgrain, *Abdom. Radiol. (NY)* **2020**, *45*, 3496, https://doi.org/10.1007/s00261-019-02338-z.

[72] T. Ichikawa, K. Sano, H. Morisaka, *Liver Cancer* **2014**, *3*, 97, https://doi.org/10.1159/000343865.

[73] M. Visentin, B. V. van Rosmalen, C. Hiller, M. Bieze, L. Hofstetter, J. Verheij, G. A. Kullak-Ublick, H. Koepsell, S. S. Phoa, I. Tamai, R. J. Bennink, T. M. van Gulik, B. Stieger, *Drug Metab. Dispos.* **2017**, *45*, 166, https://doi.org/10.1124/dmd.116.072371.

[74] B. Frosch, H. Wagener, *Nature* **1967**, *213*, 404, https://doi.org/10.1038/213404a0.

[75] N. F. LaRusso, N. E. Hoffman, A. F. Hofmann, M. G. Korman,*N. Engl. J. Med.* **1975**, *292*, 1209, https://doi.org/10.1056/NEJM197506052922303.

[76] N. W. Orntoft, O. L. Munk, K. Frisch, P. Ott, S. Keiding, M. Sorensen, *J. Hepatol.* **2017**, https://doi.org/10.1016/j.jhep.2017.02.023.

[77] N. Orntoft, K. Frisch, P. Ott, S. Keiding, M. Sorensen, *Biochim. Biophys. Acta Mol. Basis Dis*. **2018**, *1864*, 1240, https://doi.org/10.1016/j.bbadis.2017.11.016.

[78] P. Milkiewicz, S. Saksena, T. Cardenas, C. O. Mills, E. Elias, *Liver* **2000**, *20*, 330, https://doi.org/10.1034/j.1600-0676.2000.020004330.x.

[79] D. R. de Waart, S. Hausler, M. L. Vlaming, C. Kunne, E. Hanggi, H. J. Gruss, R. P. Oude Elferink, B. Stieger, *J. Pharmacol. Exp. Ther.* **2010**, *334*, 78, https://doi.org/jpet.110.166991 10.1124/jpet.110.166991.

[80] S. G. Sakka, *J. Clin. Monit. Comput*. **2018**, *32*, 787, https://doi.org/10.1007/s10877-017-0073-4.

[81] W. de Graaf, S. Hausler, M. Heger, T. M. van Ginhoven, G. van Cappellen, R. J. Bennink, G. A. Kullak-Ublick, R. Hesselmann, T. M. van Gulik, B. Stieger, *J. Hepatol*. **2011**, *54*, 738, https://doi.org/S0168-8278(10)00840-8 10.1016/j.jhep.2010.07.047.

[82] T. De Bruyn, S. Fattah, B. Stieger, P. Augustijns, P. Annaert, *J. Pharm. Sci*. **2011**, *100*, 5018, https://doi.org/10.1002/jps.22694.

[83] I. Patik, D. Kovacsics, O. Nemet, M. Gera, G. Varady, B. Stieger, B. Hagenbuch, G. Szakacs, C. Ozvegy-Laczka, *Biochem. Pharmacol*. **2015**, *98*, 649, https://doi.org/10.1016/j.bcp.2015.09.015.

[84] S. Izumi, Y. Nozaki, T. Komori, O. Takenaka, K. Maeda, H. Kusuhara, Y. Sugiyama, *Mol. Pharm*. **2016**, *13*, 438, https://doi.org/10.1021/acs.molpharmaceut.5b00664.

[85] M. Leuenberger, S. Hausler, V. Hohn, A. Euler, B. Stieger, M. Lochner, *J. Pharmacol. Exp. Ther*. **2021**, *377*, 346, https://doi.org/10.1124/jpet.120.000449.

[86] R. D. Combes, T. Berridge, J. Connelly, M. D. Eve, R. C. Garner, S. Toon, P. Wilcox, *Eur. J. Pharm. Sci*. **2003**, *19*, 1, https://doi.org/10.1016/s0928-0987(03)00040-x.

[87] G. Lappin, R. C. Garner, *Expert Opin. Drug. Metab. Toxicol*. **2008**, *4*, 1499, https://doi.org/10.1517/17425250802531767.

[88] T. Burt, K. Yoshida, G. Lappin, L. Vuong, C. John, S. N. de Wildt, Y. Sugiyama, M. Rowland, *Clin. Transl. Sci.* **2016**, *9*, 74, https://doi.org/10.1111/cts.12390.

[89] H. Shen, J. Dai, T. Liu, Y. Cheng, W. Chen, C. Freeden, Y. Zhang, W. G. Humphreys, P. Marathe, Y. Lai, *J. Pharmacol. Exp. Ther*. **2016**, *357*, 382, https://doi.org/10.1124/jpet.116.232066.

[90] D. Bednarczyk, C. Boiselle, *Xenobiotica* **2016**, *46*, 457, https://doi.org/10.3109/00498254.2015.1085111.

[91] R. R. Gilibili, S. Chatterjee, P. Bagul, K. W. Mosure, B. V. Murali, T. T. Mariappan, S. Mandlekar, Y. Lai, *Drug Metab. Dispos*. **2017**, *45*, 604, https://doi.org/10.1124/dmd.116.074740.

[92] T. T. Mariappan, H. Shen, P. Marathe, *Curr. Drug Metab*. **2017**, *18*, 757, https://doi.org/10.2174/1389200218666170724110818.

[93] X. Chu, M. Liao, H. Shen, K. Yoshida, A. A. Zur, V. Arya, A. Galetin, K. M. Giacomini, I. Hanna, H. Kusuhara, Y. Lai, D. Rodrigues, Y. Sugiyama, M. J. Zamek-Gliszczynski, L. Zhang, International Transporter Consortium, *Clin. Pharmacol. Ther*. **2018**, *104*, 836, https://doi.org/10.1002/cpt.1216.

[94] N. Tournier, B. Stieger, O. Langer, *Pharmacol. Ther*. **2018**, *189*, 104, https://doi.org/10.1016/j.pharmthera.2018.04.006.

[95] Y. Li, Z. Talebi, X. Chen, A. Sparreboom, S. Hu, *Molecules* **2021**, *26*, https://doi.org/10.3390/molecules26185500.

[96] E. Kimoto, C. Costales, M. A. West, Y. A. Bi, M. Vourvahis, A. David Rodrigues, M. V. S. Varma, *Clin. Pharmacol. Ther*. **2022**, *111*, 404, https://doi.org/10.1002/cpt.2434.

[97] B. Stieger, B. Hagenbuch, *Curr. Top. Membr*. **2014**, *73*, 205, https://doi.org/10.1016/B978-0-12-800223-0.00005-0.

[98] Y. Meier, C. Pauli-Magnus, U. M. Zanger, K. Klein, E. Schaeffeler, A. K. Nussler, N. Nussler, M. Eichelbaum, P. J. Meier, B. Stieger, *Hepatology* **2006**, *44*, 62, https://doi.org/10.1002/hep.21214.

[99] A. T. Nies, M. Niemi, O. Burk, S. Winter, U. M. Zanger, B. Stieger, M. Schwab, E. Schaeffeler, *Genome Med*. **2013**, *5*, 1, https://doi.org/gm405 10.1186/gm405.

[100] B. Prasad, R. Evers, A. Gupta, C. E. Hop, L. Salphati, S. Shukla, S. V. Ambudkar, J. D. Unadkat, *Drug Metab. Dispos*. **2014**, *42*, 78, https://doi.org/10.1124/dmd.113.053819.

[101] K. W. Peng, J. Bacon, M. Zheng, Y. Guo, M. Z. Wang, *Drug Metab. Dispos*. **2015**, *43*, 1045, https://doi.org/10.1124/dmd.115.063362.

[102] S. W. Yee, D. J. Brackman, E. A. Ennis, Y. Sugiyama, L. K. Kamdem, R. Blanchard, A. Galetin, L. Zhang, K. M. Giacomini, *Clin. Pharmacol. Ther*. **2018**, *104*, 803, https://doi.org/10.1002/cpt.1098.

[103] R. M. Cooper-DeHoff, M. Niemi, L. B. Ramsey, J. A. Luzum, E. K. Tarkiainen, R. J. Straka, L. Gong, S. Tuteja, R. A. Wilke, M. Wadelius, E. A. Larson, D. M. Roden, T. E. Klein, S. W. Yee, R. M. Krauss, R. M. Turner, L. Palaniappan, A. Gaedigk, K. M. Giacomini, K. E. Caudle, D. Voora, *Clin. Pharmacol. Ther*. **2022**, *111*, 1007, https://doi.org/10.1002/cpt.2557.

[104] M. Weiss, W. Siegmund, *J. Clin. Pharmacol.* **2021**, *61,* 506, https://doi.org/10.1002/jcph.1762.

[105] M. M. Hanczyc, P. A. Monnard, *Curr. Opin. Chem. Biol.* **2017**, *40*, 78, https://doi.org/10.1016/j.cbpa.2017.07.009.

[106] Y. Zhong, L. Yang, Y. Zhou, J. Peng, *Chem. Asian J*. **2022**, *17*, e202200038, https://doi.org/10.1002/asia.202200038.

[107] M. Bauer, A. Matsuda, B. Wulkersdorfer, C. Philippe, A. Traxl, C. Ozvegy-Laczka, J. Stanek, L. Nics, E. M. Klebermass, S. Poschner, W. Jager, I. Patik, E. Bakos, G. Szakacs, W. Wadsak, M. Hacker, M. Zeitlinger, O. Langer, *Clin. Pharmacol. Ther*. **2018**, *104*, 139, https://doi.org/10.1002/cpt.888.

[108] S. De Lombaerde, K. Kersemans, S. Neyt, J. Verhoeven, C. Vanhove, F. De Vos, *Contrast Media Mol. Imaging* **2018**, 6345412, https://doi.org/10.1155/2018/6345412.

[109] H. Kimura, Y. Yagi, K. Arimitsu, K. Maeda, K. Ikejiri, J. I. Takano, H. Kusuhara, S. Kagawa, M. Ono, Y. Sugiyama, H. Saji, *J. Labelled Comp. Radiopharm*. **2016**, *59*, 565, https://doi.org/10.1002/jlcr.3464.

[110] I. Hernandez Lozano, M. Bauer, B. Wulkersdorfer, A. Traxl, C. Philippe, M. Weber, S. Hausler, B. Stieger, W. Jager, S. Mairinger, T. Wanek, M. Hacker, M. Zeitlinger, O. Langer, *Mol. Pharm*. **2020**, *17*, 316, https://doi.org/10.1021/acs.molpharmaceut.9b01060.

[111] T. Takashima, C. Wu, M. Takashima-Hirano, Y. Katayama, Y. Wada, M. Suzuki, H. Kusuhara, Y. Sugiyama, Y. Watanabe, *J. Nucl. Med*. **2013**, *54*, 267, https://doi.org/10.2967/jnumed.112.110254.

[112] D. Vivian, K. Cheng, S. Khurana, S. Xu, P. A. Dawson, J. P. Raufman, J. E. Polli, *J. Pharm. Sci*. **2014**, *103*, 3782, https://doi.org/10.1002/jps.24131.

[113] A. Testa, S. Dall'Angelo, M. Mingarelli, A. Augello, L. Schweiger, A. Welch, C. S. Elmore, P. Sharma, M. Zanda, *Bioorg. Med. Chem*. **2017**, *25*, 963, https://doi.org/10.1016/j.bmc.2016.12.008.

[114] G. Ghibellini, E. M. Leslie, G. M. Pollack, K. L. Brouwer, *Pharm. Res*. **2008**, *25*, 1851, https://doi.org/10.1007/s11095-008-9597-0.

[115] W. de Graaf, K. P. van Lienden, T. M. van Gulik, R. J. Bennink, *J. Nucl. Med*. **2010**, *51*, 229, https://doi.org/jnumed.109.069724 10.2967/jnumed.109.069724.

[116] S. Neyt, M. Vliegen, B. Verreet, S. De Lombaerde, K. Braeckman, C. Vanhove, M. T. Huisman, C. Dumolyn, K. Kersemans, F. Hulpia, S. Van Calenbergh, G. Mannens, F. De Vos, *Nucl. Med. Biol*. **2016**, *43*, 642, https://doi.org/10.1016/j.nucmedbio.2016.07.001.
[117] M. Kobayashi, T. Nakanishi, K. Nishi, Y. Higaki, H. Okudaira, M. Ono, T. Tsujiuchi, A. Mizutani, R. Nishii, I. Tamai, Y. Arano, K. Kawai, *Nucl. Med. Biol*. **2014**, *41*, 338, https://doi.org/10.1016/j.nucmedbio.2014.01.004.
[118] M. Kobayashi, K. Nishi, A. Mizutani, T. Hokama, M. Matsue, T. Tsujikawa, T. Nakanishi, R. Nishii, I. Tamai, K. Kawai, *Sci. Rep*. **2019**, *9*, 13413, https://doi.org/10.1038/s41598-019-50049-8.
[119] M. Kobayashi, K. Nishi, A. Mizutani, H. Okudaira, T. Nakanishi, N. Shikano, R. Nishii, I. Tamai, K. Kawai, *Nucl. Med. Biol*. **2020**, *84-85*, 33, https://doi.org/10.1016/j.nucmedbio.2020.01.002.
[120] M. Kobayashi, A. Mizutani, K. Nishi, Y. Muranaka, R. Nishii, N. Shikano, T. Nakanishi, I. Tamai, E. S. Kleinerman, K. Kawai, *Nucl. Med. Biol*. **2020**, *90-91*, 49, https://doi.org/10.1016/j.nucmedbio.2020.09.004.
[121] H. Yamaguchi, M. Okada, S. Akitaya, H. Ohara, T. Mikkaichi, H. Ishikawa, M. Sato, M. Matsuura, T. Saga, M. Unno, T. Abe, N. Mano, T. Hishinuma, J. Goto, *J. Lipid Res*. **2006**, *47*, 1196, https://doi.org/M500532-JLR200 10.1194/jlr.M500532-JLR200.
[122] Y. Wang, M. Wilkerson, J. Li, W. Zhang, A. Owens, S. Wright, I. Hidalgo, *Int. J. Toxicol*. **2020**, *39*, 518, https://doi.org/10.1177/1091581820953066.
[123] K. Yamaguchi, T. Murai, H. Yabuuchi, S. P. Hui, T. Kurosawa, *Drug Metab. Pharmacokinet*. **2010**, *25*, 214, https://doi.org/10.2133/dmpk.25.214.
[124] T. De Bruyn, W. Sempels, J. Snoeys, N. Holmstock, S. Chatterjee, B. Stieger, P. Augustijns, J. Hofkens, H. Mizuno, P. Annaert, *J. Pharm. Sci*. **2014**, *103*, 1872, https://doi.org/10.1002/jps.23933.
[125] P. Martinez-Becerra, O. Briz, M. R. Romero, R. I. Macias, M. J. Perez, C. Sancho-Mateo, M. P. Lostao, J. M. Fernandez-Abalos, J. J. Marin, *Mol. Pharmacol.* **2011**, *79*, 596, https://doi.org/10.1124/mol.110.069971
[126] S. Mita, H. Suzuki, H. Akita, H. Hayashi, R. Onuki, A. F. Hofmann, Y. Sugiyama, *Drug Metab. Dispos*. **2006**, *34*, 1575, https://doi.org/10.1124/dmd.105.008748.
[127] C. Gui, A. Obaidat, R. Chaguturu, B. Hagenbuch, *Curr. Chem. Genomics* **2010**, *4*, 1, https://doi.org/10.2174/1875397301004010001.
[128] V. Szekely, I. Patik, O. Ungvari, A. Telbisz, G. Szakacs, E. Bakos, C. Ozvegy-Laczka, *Eur. J. Pharm. Sci*. **2020**, *151*, 105395, https://doi.org/10.1016/j.ejps.2020.105395.
[129] I. Patik, V. Szekely, O. Nemet, A. Szepesi, N. Kucsma, G. Varady, G. Szakacs, E. Bakos, C. Ozvegy-Laczka, *Sci. Rep*. **2018**, *8*, 2630, https://doi.org/10.1038/s41598-018-20815-1.
[130] Y. Cui, J. Konig, D. Keppler, *Mol. Pharmacol*. **2001**, *60*, 934, https://doi.org/10.1124/mol.60.5.934.
[131] C. Gui, Y. Miao, L. Thompson, B. Wahlgren, M. Mock, B. Stieger, B. Hagenbuch, *Eur. J. Pharmacol*. **2008**, *584*, 57, https://doi.org/10.1016/j.ejphar.2008.01.042.
[132] D. Bednarczyk, *Anal. Biochem*. **2010**, *405*, 50, https://doi.org/S0003-2697(10)00365-9 10.1016/j.ab.2010.06.012.
[133] K. Heredi-Szabo, E. Kis, E. Molnar, A. Gyorfi, P. Krajcsi, *J. Biomol. Screen.* **2008**, *13*, 295, https://doi.org/10.1177/1087057108316702.
[134] T. G. Tucker, A. M. Milne, S. Fournel-Gigleux, K. S. Fenner, M. W. Coughtrie, *Biochem. Pharmacol*. **2012**, *83*, 279, https://doi.org/10.1016/j.bcp.2011.10.017.
[135] S. Ohtsuki, O. Schaefer, H. Kawakami, T. Inoue, S. Liehner, A. Sato, N. Ishiguro, W. Kishimoto, E. Ludwig-Schwellinger, T. Ebner, T. Terasaki, *Drug Metab. Dispos*. **2012**, *40*, 83, https://doi.org/10.1124/dmd.111.042259.
[136] A. K. Deo, B. Prasad, L. Balogh, Y. Lai, J. D. Unadkat, *Drug Metab. Dispos.* **2012**, *40*, 852, https://doi.org/10.1124/dmd.111.043810.
[137] B. Prasad, Y. Lai, Y. Lin, J. D. Unadkat*, J. Pharm. Sci*. **2013**, *102*, 787, https://doi.org/10.1002/jps.23436.
[138] L. Wang, B. Prasad, L. Salphati, X. Chu, A. Gupta, C. E. Hop, R. Evers, J. D. Unadkat, *Drug Metab. Dispos*. **2015**, *43*, 367, https://doi.org/10.1124/dmd.114.061580.
[139] B. D. van Groen, E. van de Steeg, M. G. Mooij, M. M. H. van Lipzig, B. A. E. de Koning, R. M. Verdijk, H. M. Wortelboer, R. Gaedigk, C. Bi, J. S. Leeder, R. H. N. van Schaik, J. van Rosmalen, D. Tibboel, W. H. Vaes, S. N. de Wildt, *Eur. J. Pharm. Sci*. **2018**, *124*, 217, https://doi.org/10.1016/j.ejps.2018.08.042.
[140] C. Y. Li, C. Hosey-Cojocari, A. Basit, J. D. Unadkat, J. S. Leeder, B. Prasad, *AAPS J.* **2019**, *21*, 88, https://doi.org/10.1208/s12248-019-0359-1.
[141] N. Couto, Z. M. Al-Majdoub, B. Achour, P. C. Wright, A. Rostami-Hodjegan, J. Barber, *Mol. Pharm*. **2019**, *16*, 632, https://doi.org/10.1021/acs.molpharmaceut.8b00941.
[142] A. Vildhede, J. R. Wisniewski, A. Noren, M. Karlgren, P. Artursson, *J. Proteome Res*. **2015**, *14*, 3305, https://doi.org/10.1021/acs.jproteome.5b00334.
[143] C. Wegler, L. Prieto Garcia, S. Klinting, I. Robertsen, J. R. Wisniewski, J. Hjelmesaeth, A. Asberg, R. Jansson-Lofmark, T. B. Andersson, P. Artursson, *Clin. Pharmacol. Ther*. **2021**, *109*, 762, https://doi.org/10.1002/cpt.2056.
[144] J. Barber, Z. M. Al-Majdoub, N. Couto, A. M. Vasilogianni, A. Tillmann, S. Alrubia, A. Rostami-Hodjegan, B. Achour, *Drug Metab. Dispos*. **2022**, *50*, 762, https://doi.org/10.1124/dmd.121.000780.

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