

# The relevance of hepatobiliary elimination in pharmacokinetics

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Transport proteins mediating the uptake and efflux of small molecules across hepatocellular membrane domains are key determinants of hepatobiliary elimination, and thus of the half-life of many drugs and endogenous substances in blood plasma. Uptake transporters with overlapping substrate specificity and localized to the basolateral (sinusoidal) membrane of human hepatocytes include the organic anion transporters OATP1B3 (OATP8), OATP1B1 (OATP-C), and OATP2B1 (OATP-B). Subsequent to the uptake of drugs and possible phase I and phase II reactions, the necessary and final step in elimination and detoxification is predominantly mediated by members of the multidrug resistance protein subfamily of ABC transporters (MRPs or ABCCs), particularly by the apical export pump MRP2 (ABCC2), resulting in the efflux of conjugates into the extracellular space. Several mutations in the *ABCC2* gene have been identified which lead to the absence of transport-active MRP2 from the canalicular membrane and to conjugated hyperbilirubinemia (1). In vivo studies in *Abcc2*-deficient mutant rats illustrate the pharmacokinetic importance of this ABC transporter. Basolateral efflux from the hepatocyte of many organic anions, including drugs conjugated with glu-

tathione or with glucuronate, can be mediated by MRP3 and MRP4.

*In vitro* systems for studies on transport include double- and multiple- transfected polarized cells permanently expressing one or more human uptake transporters, possibly a phase-II conjugation enzyme, and the apical export pump MRP2 (2). These multiple-transfected cell lines have served to demonstrate the importance of transport proteins in hepatobiliary elimination of drugs and endogenous substances and to examine inhibitory side effects of drugs and drug candidates.

## References

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