Bile Salt Export Pump (BSEP) Gene Repression in Drug-Induced Cholestatic Liver Injury
B. Garzel ¹, H. Yang ¹, C. Lynch ¹, L. Zhang ², S-M. Huang ², J. Polli ¹, H. Wang ¹
¹ University of Maryland, ² U.S. Food and Drug Administration

Purpose
The bile salt export pump (BSEP, ABCB11) is predominantly responsible for the efflux of bile salts. Disruption of BSEP function is often associated with altered hepatic homeostasis of bile acids and cholestatic liver injury. Accumulating evidence suggests that many drugs can cause cholestasis through their interactions with transporters. To date, a relatively strong association between drug-induced cholestasis and attenuated BSEP activity has been proposed. However, whether repression of BSEP transcription would contribute to drug-induced cholestasis, is largely unknown. In this study, we have selected 30 drugs, previously reported to inhibit BSEP, to evaluate their effects on BSEP expression in human primary hepatocytes.

Methods
Sandwich-cultured human primary hepatocytes were treated with selected drugs or vehicle control. Real-time PCR and Western blotting analyses were used to measure the mRNA and protein expression of BSEP. Drugs with significant influence on the expression of BSEP were subjected to concentration-dependent evaluations. A cell-based FXR activation assay was employed to measure FXR-dependent expression of BSEP. Efflux function of BSEP was evaluated in cells over-expressing human BSEP.

Results
Our results indicate that among drugs with a known IC50 ≤ 25µM, some (e.g., lopinavir) strongly repress the expression of BSEP, while others (e.g., cyclosporine-A) had negligible effects. Upon further investigation in a concentration-dependent manner, it was determined that the transcriptional repression of BSEP by lopinavir occurs, at least in part, through its interaction with FXR. Using a human primary hepatocyte model for bile acid accumulation, we found an accumulation of bile acid in hepatocytes, though moderate, upon treatment with BSEP inhibitors/repressors.

Conclusion
Our data suggests that repression of BSEP expression may play a role in drug-induced cholestatic liver toxicity. Repression should be considered along with inhibition of BSEP, as the combination of the two reveal a more accurate prediction of cholestasis, than do either repression or inhibition alone. Investigation of BSEP function in new drug applications may be beneficial in avoiding potentially cholestatic drug candidates.