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LETTER TO THE EDITOR

Response to the Comment on the Article "Physiologically Based Modeling of Pravastatin Transporter-Mediated Hepatobiliary Disposition and Drug-Drug Interactions"

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To the Editor:

We appreciated the letter by Neuhoff and Tucker, which corroborated the methodology adopted in our recent study, "Physiologically based modeling of pravastatin transporter-mediated hepatobiliary disposition and drug-drug interactions" (1), while providing further comments on the scope of 'bottom-up' prediction of transporter-mediated drug-drug interactions (DDIs). We agree that there is a growing knowledge in the *in vitro-in vivo* extrapolation (IVIVE) of transporter data, which could facilitate a comprehensive "bottom-up" approach in the future. However, there are considerable knowledge gaps at this stage which made us adopt a 'middle-out" approach, wherein, a whole-body physiologically based pharmacokinetic (PBPK) model was developed based majorly on preclinical data and later refined using clinical pharmacokinetic data.

The apparent discrepancy in the active transport kinetics could be qualitatively justified by the differences in the protein expression levels. For example, sandwich cultured human hepatocyte (SCHH) system showed up-regulated MRP2, but down-regulated OATP transporters, based on the protein quantification generated in our laboratory (2, 3). Although a ~5-fold higher MRP2 expression in SCHH could justify the scaling factor estimated for canalicular efflux of pravastatin, such direct translation is not apparent for sinusoidal uptake transporters (OATPs relative expression factor ~2-7 (2) *versus* scaling factor ~31(1)). In fact, based on our previous studies (4), the scaling factors derived using similar approach seem to be compound-specific, which suggests the need to understand differences in both transporter expressions, as well as transporter functional activity of the *in vitro* experimental systems compared to that *in vivo*. Collectively, protein quantification data are undoubtedly essential for model building and provide confidence in the translation of *in vitro* parameters, however, the discrepancies in IVIVE cannot be explained by only considering transporter expression levels. While further understanding in this area is warranted, we strongly believe that refining the mechanistic model based on clinical pharmacokinetic data provides the confidence necessary to make quantitative DDI predictions.

The estimated *in vivo* Ki values for cyclosporine and gemfibrozil are more potent compared to mean *in vitro* values. Interestingly, this trend is consistent with the CYP-mediated DDIs, where relatively large differences were noted between the *in vitro* and *in vivo* Ki values for lipophilic inhibitors (5). Nevertheless, we note that the estimated *in vivo* Ki values also predicted DDIs for other OATP1B1 substrate drugs (6). We agree that the discrepancies between *in vitro* and *in vivo* Ki demand for careful considerations, with an emphasis on elucidating the mechanism of inhibition (competitive *versus* possible time-dependent inhibition). However, lack of data on interaction parameters such as K_{deg} (degradation rate constant) for drug transporters precludes incorporation of time-dependent inhibition mechanism in transporter DDI predictions.

Finally, the other major challenge in prospective predictions of the transporter-mediated DDIs is sparse availability of the clinical interaction data to validate the mechanistic models. As noted by Neuhoff and Tucker, the majority of interaction studies of various statins with cyclosporine were done in a organ-transplant patient population, who may not only have altered physiology but may also exhibit down-regulation of drug transporters and metabolic enzymes. While the influence of elevated cytokines on transporter activity is not completely understood *in vivo*, decreasing the relative expression factor in the model for organ-transplant

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patients will further underestimate the magnitude of DDIs, as a consequence of decreased contribution of transporter-mediated hepatic disposition. Arguably, differences in transporter activity alone may not explain the exposure difference of OATPs substrates in different ethnic populations (7), and requires further comprehensive investigations. Nevertheless, considerations of ethnic differences and other endogenous regulators of transporter activity are expected to improve quantitative DDI predictions.

While the knowledge on the role of drug transporters in ADME is rapidly growing, there is not enough mechanistic understanding of the systems to efficiently de-risk DDIs using a purely "bottom up" PBPK modeling approach. Therefore, we advocate a "middle-out" approach incorporating both preclinical and clinical pharmacokinetic data, which provides greater confidence in the prospective predictions of transporter-mediated DDIs.

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