Evaluating the Translatability of Rifampin-Tamoxifen Drug Interaction in Humanized PXR-CAR-CYP3A4/3A7-CYP2D6 Mouse Model to the Observed Clinical Drug Interaction

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Purpose
Assessing potential drug-drug interaction (DDI) liability in the clinic is an important component during drug discovery and development. However, animal models are not typically used to assess DDI because of poor translatability to the clinic due to possible species differences that may exist in drug elimination and regulation pathways. Recently, animal models expressing the human protein orthologs such as PXR and CYP isoforms have become available. The purpose of this work was to investigate the utility of the humanized mouse models, specifically to evaluate its translatability of the rifampin-tamoxifen drug interaction observed in the clinic.

Methods
Humanized PXR-CAR-CYP3A4/3A7-CYP2D6 animals either received vehicle or 50 mg/kg/day rifampin orally for 3 days (N=4). One the fourth day, 20 mg/kg of tamoxifen was orally administered to all animals. Blood was sampled at multiple timepoints and mass spectrometry was used to quantitate tamoxifen and its metabolites 4-hydroxy tamoxifen (4OHT), N-desmethyl tamoxifen (NDM), E-endoxifen (EEXN) and Z-endoxifen (ZEXN).

Results
Tamoxifen was extensively metabolized, yielding metabolite/parent ratio (MP) for 4OHT, NDM, EEXN and ZEXN at 4.1, 1.0, 0.20 and 2.2, respectively. Following treatment with rifampin, tamoxifen AUC decreased 4-fold compared to the vehicle-treated animals, from 0.824 to 0.195 µM*hr. Absolute metabolite exposure was not significantly changed, but MP increased to 15, 3.1, 1.5 and 8.0 for 4OHT, NDM, EEXN and ZEXN, respectively.

Conclusion
Tamoxifen is metabolized by CYP3A4 and CYP2D6. In the clinic, multiple day treatment of rifampin decreased tamoxifen AUC by 6-fold, and interestingly, its metabolites NDM, 4OHT and endoxifen also decreased by 3-fold, to yield only 2-fold increases in MP (Binkhorst et al., 2012). The humanized model was able to mimic the magnitude of tamoxifen decrease observed in the clinic. Although the model underestimated the extent of change of metabolites, it did correctly show that metabolites did not increase and mirrored the moderate MP increase. These data suggest that the humanized mice may be a suitable model to estimate the extent of tamoxifen modulation from rifampin induction.