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ARTICLE IN REVIEW:

TruVivo® Delivers Quantitative Clinical Drug Interaction Predictions via All-Human Hepatocyte Triculture Platform

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TITLE: Quantitative clinical risk assessment of CYP2C, UDP-glucuronosyltransferase, P-glycoprotein induction, and complex drug-drug interactions using TruVivo human hepatocyte triculture platform.

AUTHOR(S): Ramsden D, Fullenwider CL, Cipriano S, LeCluyse EL

STUDY DESIGN: *In vitro* experimental validation study

SUMMARY: Current *in vitro* systems often lack sufficient dynamic range to reliably predict clinical induction of enzymes and transporters beyond CYP3A, leaving uncertainty in assessing drug–drug interaction (DDI) risk—particularly for compounds that exhibit both induction and inhibition or that affect coregulated pathways such as CYP2C enzymes, UGT1A4, and P-glycoprotein.

This study evaluated the TruVivo 2D+ hepatic model as an *in vitro* system for quantitative assessment of induction-based DDIs. Using known clinical inducers, concentration-dependent changes in mRNA and enzyme activity across two hepatocyte donors were characterized. Induction parameters for comparison with observed clinical area-under-the-curve ratios (AUCR) were generated. Additional experiments assessed the model's ability to reproduce net outcomes for complex DDIs involving simultaneous induction and inhibition.

The model produced consistent and measurable induction across CYP2C8, CYP2C9, CYP2C19, CYP3A4, UGT1A4, and P-gp. Predicted AUCR values aligned with clinical observations across most inducer–substrate pairs. *In situ* experiments reproduced the direction and relative magnitude of substrate-dependent net effects for combined inducer/inhibitor precipitants.

Overall, the data support TruVivo as a translational *in vitro* tool for evaluating induction-based DDIs and for investigating complex interaction mechanisms.

TruVivo provides quantifiable induction across multiple clinically relevant pathways

TruVivo demonstrated concentration-dependent induction of CYP2C8, CYP2C9, CYP2C19, CYP3A4, UGT1A4, and P-gp using a diverse set of clinical inducers. The model produced induction magnitudes that enabled parameter estimation across donors, addressing the limited responsiveness typically observed in monoculture hepatocytes.

Improved alignment between *in vitro* induction and clinical AUCR

Induction parameters generated in TruVivo, when applied to static prediction models, reproduced clinical AUCR values for most enzyme–substrate pairs. The quantitative relationship between observed induction and clinical outcome supports the model's utility for informing DDI risk assessment and potentially reducing the need for certain clinical interaction studies.

Ability to characterize complex induction–inhibition interactions

In situ DDI studies using precipitants with known substrate-dependent clinical effects (e.g., ritonavir, efavirenz, nelfinavir) yielded outcomes consistent with reported clinical data. The model captured both directionality and relative magnitude of net effects, indicating suitability for evaluating compounds where concurrent induction and inhibition complicate standard prediction approaches.

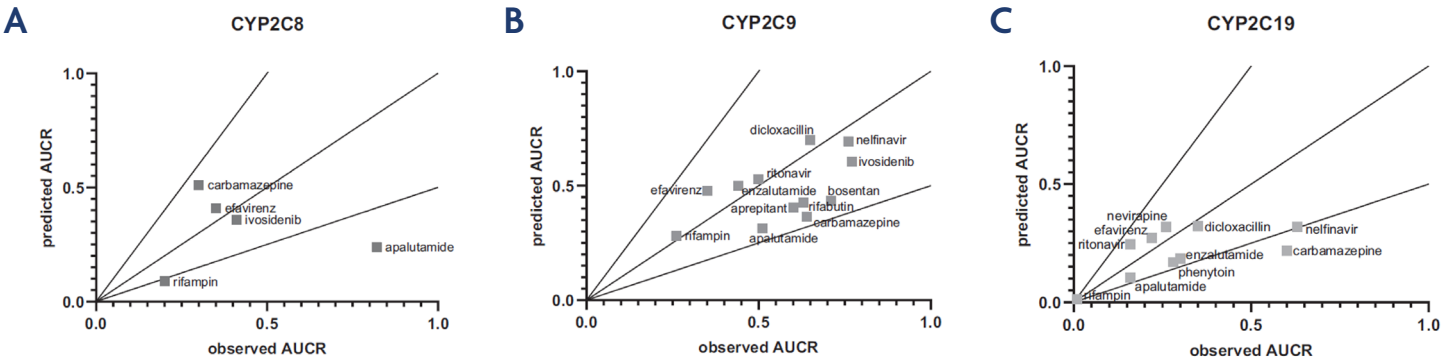

Figure 1. *In vitro–in vivo* extrapolation (IVIVe) of CYP2C induction using TruVivo (Donor 1). Predicted area-under-the-curve ratios (AUCR) derived from TruVivo induction parameters are plotted against clinically observed AUCR values for CYP2C8 (A), CYP2C9 (B), and CYP2C19 (C). Each point represents a precipitant–substrate pair with available clinical data. The solid line denotes unity, and dashed lines indicate a twofold prediction error range. TruVivo predictions for CYP2C enzymes aligned with clinical outcomes across most inducers, supporting the model's utility for quantitative assessment of induction-based drug–drug interactions. Image reproduced with permission under an open access license.[1]

References

1. **Diane Ramsden, Cody L. Fullenwider, Cipriano Santos, Edward L. LeCluyse. (2025).** Quantitative clinical risk assessment of CYP2C, UDP-glucuronosyltransferase, P-glycoprotein induction, and complex drug-drug interactions using TruVivo human hepatocyte triculture platform. Drug Metabolism and Disposition, 53, 100052.