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TruVivo® Application Brief: **A Human-Relevant Model for CYP2C Induction and DDI Risk Assessment**

The Research Challenge

Regulatory is placing more pressure on pharma companies to understand the translation of *in vitro* positive CYP3A4 induction results to other pathways co-regulated with CYP3A including other CYPs, UGTs and transporters. **Standard hepatocyte monoculture models fail** to capture the clinically observed induction potential of **CYP2C enzymes (CYP2C8, CYP2C9, CYP2C19).**

Dynamic range is limited (< 2-fold mRNA increase for rifampicin) – forcing industry to infer CYP2C risk from CYP3A4 data. This has led to **underprediction of potential clinical DDI risk** and uncertainty in regulatory submissions.

Researchers need a model that more accurately represents human CYP2C induction dynamics and allows IVIVE and PBPK modeling approaches to inform clinical outcomes.

The TruVivo® Solution

An advanced human hepatic triculture model of all-human primary cells — hepatocytes supported by stromal and endothelial feeder cells — delivering sustained function, reproducibility, and significantly improved nuclear receptor signaling for generating accurate, reproducible CYP induction data.

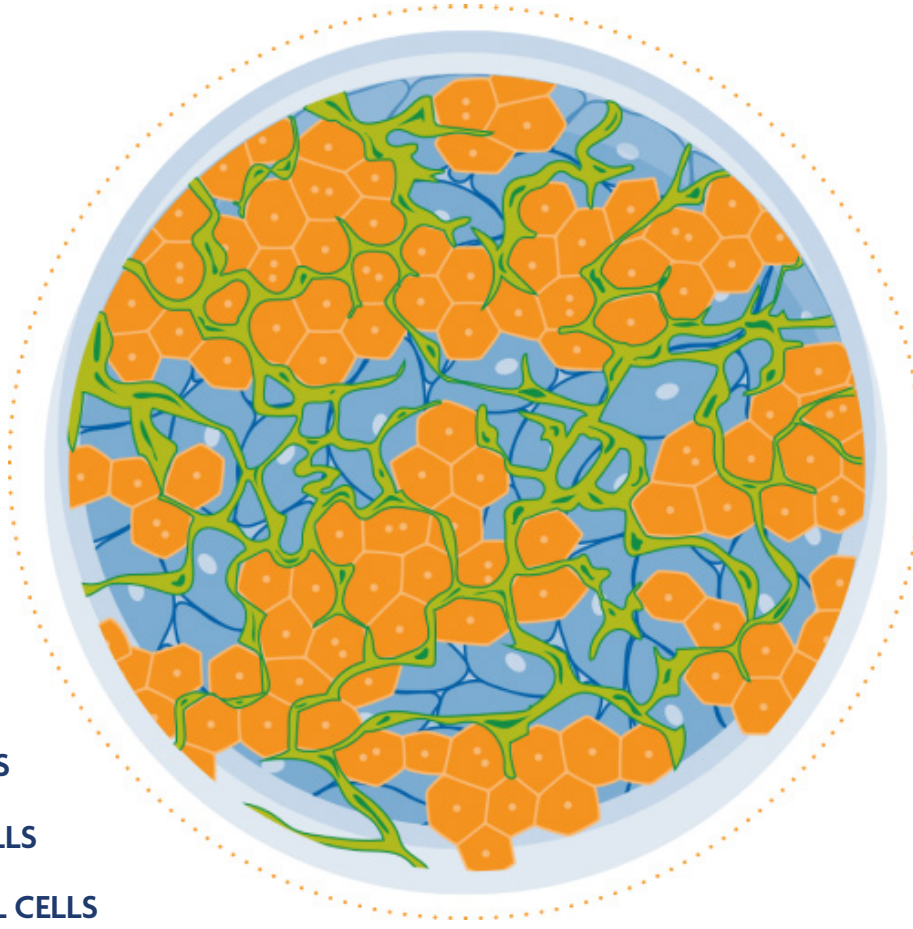
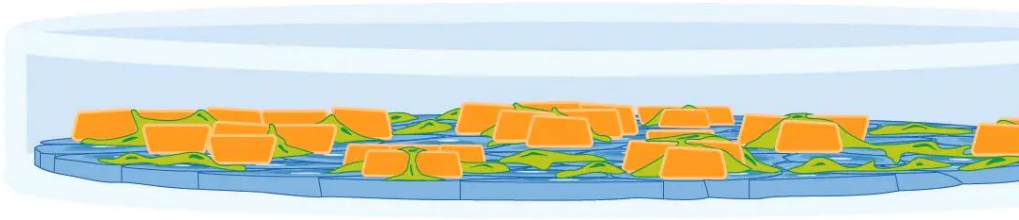


Figure legend: Schematic representation of TruVivo showing top and side view of the self-assembled, multicellular hepatocyte colonies integrated among a mixed feeder cell layer.



Key Findings and Validation

Finding	Evidence
Robust and reproducible CYP2C induction	• Rifampicin, apalutamide, efavirenz, and carbamazepine produced **concentration-dependent increases** in CYP2C8, CYP2C9, and CYP2C19 mRNA and activity across three donors[2]. • E_{max} up to **8–20× (CYP2C8/19) and 2–4× (CYP2C9)** — exceeding the <2-fold dynamic range of conventional hepatocyte systems[2].
Improved CYP2C19 expression vs. 2D culture	• TruVivo maintained **CYP2C19 gene expression 4–6× higher** than 2D sandwich culture hepatocytes, enabling quantifiable induction responses not measurable in standard systems[2].
Quantitative translation to clinical outcomes*	• TruVivo-derived induction parameters achieved **AUCR predictions within 2-fold of clinical data** for >80% of CYP2C substrates[2]. • For CYP2C9 and CYP2C8, **85% and 64%** of induction predictions captured ≥80% of observed clinical effects[1]. • Supported **accurate IVIVE** for CYP3A4, CYP2C19, UGT1A4, and P-gp induction pathways[1].
PBPK modeling confirms predictive performance	• Integration of TruVivo data into **Simcyp PBPK** models produced **excellent alignment with clinical pharmacokinetic profiles[2].** • Outperformed mechanistic static models (MSM) by reducing over- and under-prediction of DDI magnitude[2]. • Enabled full **concentration–time profile prediction** for victim drugs such as omeprazole, tolbutamide, and glyburide[2].
Cross-laboratory reproducibility	• Independent studies demonstrated **<2-fold variability** in CYP2C induction response across laboratories using TruVivo[1] — compared to >10-fold variability typical of 2D hepatocyte cultures.
Multi-pathway and complex DDI modeling	• TruVivo accurately predicted **net induction and inhibition outcomes** for co-inducer/inhibitor compounds (e.g., **ritonavir**)[1]. • Maintained **PXR/CAR signaling fidelity**, allowing concurrent evaluation of CYP2C, CYP3A4, UGT, and transporter induction[1].
Consistent donor performance	• CYP2C induction EC_{50} and E_{max} values were **highly consistent across donors**, minimizing inter-donor variability[2]. • Stable phenotype and nuclear receptor responsiveness sustained throughout extended culture[2].

*CYP2C19, CYP3A4, UGT1A4, and P-gp all showed quantitative IVIVE correlation, typically within 2-fold of observed AUCRs once GMFE correction was applied for CYP2C19 and CYP3A4.

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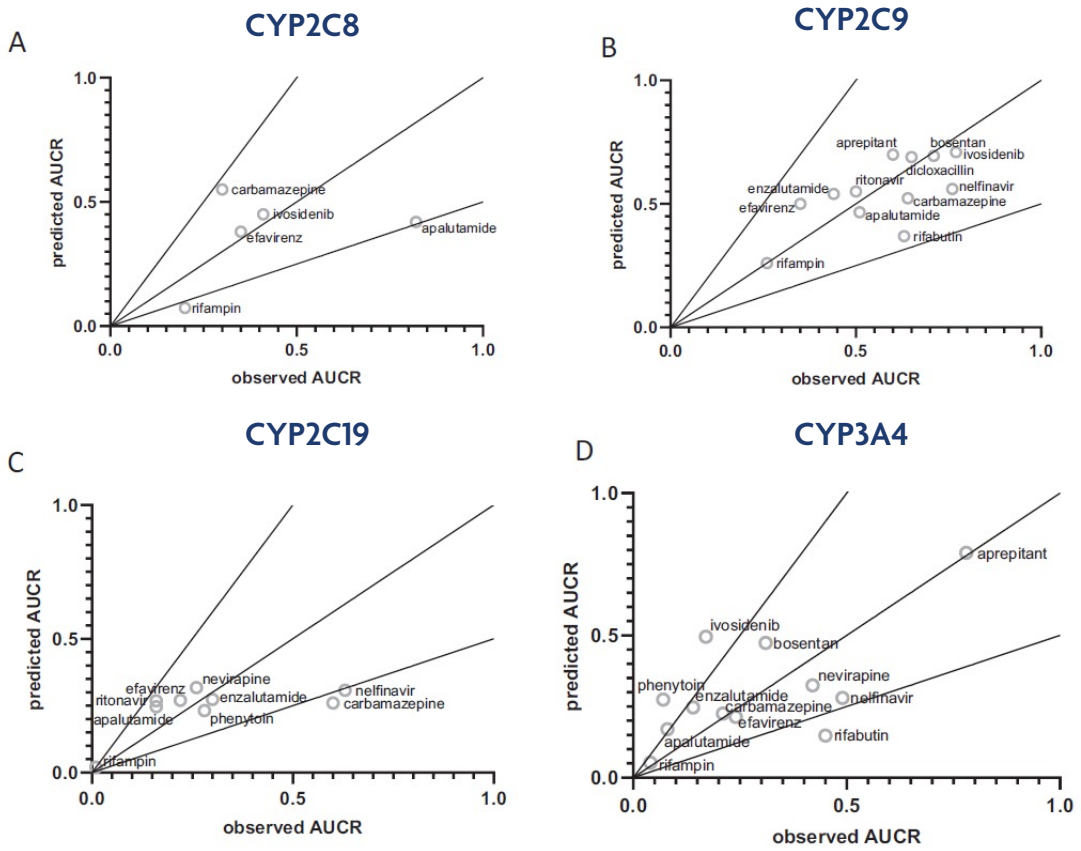

Figure legend: **Predictive accuracy of *in vitro–in vivo* extrapolation (IVIVE) for CYP2C8, CYP2C9, CYP2C19, and CYP3A4**
Model predictions using averaged donor (n=2) data closely align with clinical outcomes, demonstrating strong translational performance. The central line shows perfect prediction, with upper and lower lines marking a two-fold range. GMFE corrections were applied for CYP2C19 and CYP3A4 to refine accuracy. Figure reproduced from portions of Figure 6 of Ramsden et al. with permission under an open access license.[1]

Why Researchers Choose TruVivo

Researchers Need	TruVivo Advantage
Predictive Accuracy	Clinically aligned CYP2C induction responses — AUCR predictions within 2-fold of observed clinical outcomes for >80% of test compounds, including CYP2C8, CYP2C9, CYP2C19, CYP3A4, UGT1A4, and P-gp[1,2].
Nuclear Receptor Biology	Authentic human cellular composition and architecture sustain **endogenous PXR and CAR activation**, driving physiologic regulation of CYP2C isoforms and accurate induction magnitude[1,2].
Long-term Stability	Maintains hepatocyte phenotype and enzyme function for **multi-day exposures and repeated dosing**, enabling concentration-response studies and chronic DDI modeling[2].

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Multi-enzyme and Transporter Insight	Parallel evaluation of **CYP2C, CYP3A, UGT, and P-gp** induction within the same culture — supporting integrated mechanistic modeling of hepatic metabolism and clearance[1].
Cross-lab Reproducibility	Demonstrated **<2-fold variability** in induction magnitude across independent laboratories, compared with >10-fold variability typical of 2D hepatocyte systems[1].
Complex DDI Modeling Capability	Successfully predicted **net induction and inhibition outcomes** for dual-acting compounds such as **ritonavir**, enabling realistic assessment of competing metabolic pathways[1].
Industry Validation	Independently evaluated and published by leading pharma collaborators (AstraZeneca, IQ Induction Working Group) as a reliable tool for **quantitative IVIVE of CYP2C-mediated DDI risk[1,2].**

Research Applications

- Induction risk assessment for **CYP2C enzymes** (CYP2C8/9/19)
- **Clinical DDI prediction** and quantitative IVIVE modeling
- Mechanistic studies of **nuclear receptor activation pathways**
- Early de-risking for **co-inducer/inhibitor compounds**

References

1. **Ramsden D.,** Fullenwider C.L., Santos C., LeCluyse E.L. (2025) Quantitative Clinical Risk Assessment of CYP2C, UGT, and P-gp Induction Using the TruVivo Human Hepatocyte Triculture Platform. Drug Metab Dispos 2025.

2. **Slavsky M.,** Karve A.S., Hariparsad N. Physiologically Based Pharmacokinetic Modeling to Assess Perpetrator and Victim CYP2C Induction Risk. Pharmaceutics 2025, 17(1085).

Learn how TruVivo can transform your DDI and induction studies.

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