

Supplementary Information

Acetaminophen cytotoxicity is ameliorated in a human liver organotypic co-culture model

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Supplementary Information Table S1 Hepatic-specific function in different in vitro culture systems compared with primary human hepatocytes

Culture system (2D format unless stated)	Albumin μg/hr/million cells (unless stated)	CYP450s: CYP3A4 unless stated (Activity/ Inducibility/ Functionality)	Response to Acetaminophen (APAP) Toxicity	References / Comment
Primary human Hepatocytes (PHHs) (mono-culture)	0.05-0.8 (subject to donor variability)	High	Yes (sensitive)	(Chesne 1993, Lübberstedt, Müller-Vieira et al. 2011)
PHHs (mono-culture) Micropatterned cocultures (PHHs:mouse fibroblasts)	0.01 (d3) 0.5 (d1) 1.0 (d3)	High	Yes (sensitive)	(Khetani and Bhatia 2008)
PHHs (mono-culture) PHHs:HUVECs co-culture	0.001 (d3) 0.003 (d3)	CYP3A4 (diazepam metabolites)	ND	(Salerno, Campana et al. 2011)
PHH-MPCCs (PHH-based micro-patterned co-cultures containing mouse 3T3-J2 fibroblasts)	6-7 (> in vivo rates) (subject to donor variability)	High Transcriptome comparable with fresh PHHs; & PHH-MPCCs	Yes (sensitive to multiple dosing)	(Berger, Ware et al. 2015)
C3A monoculture	*1.0	ND	ND	(Filippi, Keatch et al. 2004)
C3A monoculture Co-culture (C3A:HUVECs)	0.83 1.42	Low drug metabolizing enzymes (DMEs) (2.5x fold increase in co-culture)	Yes (low in C3A mono-culture); High sensitivity in HUVEC mono-cultures	Present study (see Fig. 2)
HepG2 mono (static) Co-culture (static) (HepG2:HUVECs) HepG2 mono (bioreactor) Co-culture (bioreactor)	0.01 0.03 0.015 0.05	Very low (DMEs) in mono	No (insensitive)	(Guzzardi, Vozzi et al. 2009)

Rat hepatocytes monoculture Hepatocytes/LSEC co-culture hepatocytes/LSEC/fibroblast tri-culture	3.0 µg/day 1.0 µg/day 11.0 µg/day	ND	ND	(March, Hui et al. 2009)
Rat hepatocytes monoculture Co-culture Rat hepatocytes:bovine carotid artery (ECs)	0.5 (d1); 0.2 (d7) 0.6 (d1) 1.0 (d7)	ND	ND	(Kim, Ohashi et al. 2012)
HepaRG co-culture 2D (3D) (Hepatocytes:cholangiocytes) 2D*	0.21 (0.49) *0.15	High (120% of PHH value)	Yes (Sensitive)	(Lübberstedt, Müller-Vieira et al. 2011, Leite, Wilk-Zasadna et al. 2012)
In vivo values: (human liver) (rat liver)	2.0 2.4	184* 292* [Total P450 content (pmol/ mg TP)]	Yes (sensitive)	(Gómez-Lechón, López et al. 1990, Lazar, Mann et al. 1995, Donato, Castell et al. 1999, Iwata, Sajiki et al. 1999)
HUVECs	ND	CYP2E1 transcripts' constitutive expression	ND	(Farin 1994)

Table S1 Hepatic-specific function/ expression in different in vitro culture systems compared with primary human hepatocytes, in vivo (liver) data from different species and HUVECs. Several factors including culture protocols (eg cell type/ species used) hepatic functions, culture conditions and duration vary greatly between research groups makes direct comparisons difficult. For clarity, mean values are shown. In vivo values are shown for human and rat livers. Abbreviations: ND, not determined in referenced study. ND, Not determined or not measured.

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