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ERRATUM

The article shown below was originally published in Volume 19, Number 3, pages 199–214 (doi: https://doi.org/10.3727/105221619X15638857793317). Some information shown in Table 1 appeared incorrectly in the C_{max} column. The table has been corrected in the online version, and the corrected table is also shown here.

Long-Term Engineered Cultures of Primary Mouse Hepatocytes for Strain and Species Comparison Studies During Drug Development

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Testing drugs in isogenic rodent strains to satisfy regulatory requirements is insufficient for derisking organ toxicity in genetically diverse human populations; in contrast, advances in mouse genetics can help mitigate these limitations. Compared to the expensive and slower in vivo testing, in vitro cultures enable the testing of large compound libraries toward prioritizing lead compounds and selecting an animal model with human-like response to a compound. In the case of the liver, a leading cause of drug attrition, isolated primary mouse hepatocytes (PMHs) rapidly decline in function within current culture platforms, which restricts their use for assessing the effects of longer-term compound exposure. Here we addressed this challenge by fabricating mouse micropatterned cocultures (mMPCC) containing PMHs and 3T3-J2 murine embryonic fibroblasts that displayed 4 weeks of functions; mMPCCs created from either C57Bl/6J or CD-1 PMHs outperformed collagen/Matrigel™ sandwich-cultured hepatocyte monocultures by ~143-fold, 413-fold, and 10-fold for albumin secretion, urea synthesis, and cytochrome P450 activities, respectively. Such functional longevity of mMPCCs enabled in vivo relevant comparisons across strains for CYP induction and hepatotoxicity following exposure to 14 compounds with subsequent comparison to responses in primary human hepatocytes (PHHs). In conclusion, mMPCCs display high levels of major liver functions for several weeks and can be used to assess strain- and species-specific compound effects when used in conjunction with responses in PHHs. Ultimately, mMPCCs can be used to leverage the power of mouse genetics for characterizing subpopulations sensitive to compounds, characterizing the degree of interindividual variability, and elucidating genetic determinants of severe hepatotoxicity in humans.

Key words: Micropatterned cocultures; Drug-induced liver injury; Murine embryonic fibroblasts; Cytochrome P450; Sandwich cultures

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Table 1. IC_{50} Values for Compounds Tested in Primary Mouse and Human Hepatocytes in Micropatterned Cocultures (MPCCs)

		Albumin			Urea			Cell Viability			ATP		
Compound	C_{max} (μM)	CD-1	C57	Human	CD-1	C57	Human	CD-1	C57	Human	CD-1	C57	Human
Diclofenac	8.023	43.6 ± 28.4	56.1 ± 6.8	57.0 ± 7.6	53.2 ± 2.0	48.7 ± 12.4	44.0 ± 26.2	71.6 ± 8.6	73.0 ± 0.7	37.6 ± 32.2	59.8 ± 3.0	63.9 ± 1.9	37.1 ± 34.8
Fialuridine	1.000	–	–	40.7 ± 30.8	–	–	13.6 ± 1.4	–	–	80.4 ± 0.1	–	–	79.7 ± 7.8
Ibufenac	100.000	–	–	66.8 ± 23.3	–	–	54.7 ± 4.5	–	–	75.4 ± 30.8	–	–	70.4 ± 41.9
Nefazodone	1.000	76.5 ± 3.6	58.8 ± 9.1	37.6 ± 35.2	77.9 ± 31.3	76.7 ± 10.0	28.4 ± 22.2	73.3 ± 1.5	73.6 ± 1.1	38.2 ± 35.7	80.3 ± 27.9	60.3 ± 0.6	37.6 ± 35.5
Tolcapone	18.000	62.6 ± 14.8	37.8 ± 32.1	18.6 ± 8.6	56.3 ± 9.0	37.3 ± 32.6	28.4 ± 22.5	55.8 ± 14.5	49.1 ± 37.9	31.0 ± 24.9	62.5 ± 0.1	37.7 ± 33.2	36.2 ± 33.3
Troglitazone	6.387	–	63.6 ± 4.5	77.8 ± 31.4	–	80.5 ± 27.7*	42.73 ± 28.0	–	85.8 ± 20.1	77.89 ± 18.8	–	67.2 ± 15.4	60.7 ± 52.9
Buspirone	0.005	–	–	–	–	–	–	–	–	–	–	–	–
Rosiglitazone	1.120	–	–	–	–	–	–	–	–	–	–	–	–
Warfarin	4.868	–	–	–	–	–	–	–	–	–	–	–	–

Values listed are IC_{50} values (average ± standard deviation from $n = 2$ donors), the interpolated drug concentration that reduces a biochemical signal by 50%, presented as multiples of C_{max} (maximum concentration observed in human plasma). "–" represents an IC_{50} value above 100 × C_{max} (i.e., could not be interpolated from the dose range tested here) and declared to be "nonhepatotoxic" by our algorithm. C57 refers to the C57Bl/6J mouse strain. Italicized drug names represent nonhepatotoxic drugs, while the nonitalicized drugs are typically considered hepatotoxins in humans. There are no statistically significant differences in interpolated IC_{50} values comparing human to mouse and across mouse strains based on a one-way ANOVA analysis.