



Ex Vivo Induction Studies

The isoforms of the cytochrome P450 (CYP) family are the key enzymes of drug metabolism¹. CYP enzyme induction caused by one drug may result in the increased metabolism of a co-administered drug, resulting in drug-drug interactions². Additionally, enzyme induction can increase the toxicity of some xenobiotics or enhance the tolerance to other toxicants.

To study the CYP induction potential of a drug candidate, we prepare microsomes from liver tissue of animals dosed with a drug candidate *in vivo*. The microsomes are analyzed for dose-dependent changes in total CYP levels and specific CYP-dependent enzyme activities.

Increasing discovery. Advancing development.



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Experimental Features

- Test system: liver microsomes prepared from NME-treated animals
- Analysis of liver microsomes for protein content, total CYP levels, and specific CYP enzyme activities
- All known major inducible CYP enzymes are evaluated
- Specific CYP substrates are used to account for species differences in enzyme induction

Species-Specific CYP Enzyme Assays

Species	CYP1A	CYP2B	CYP2E1	CYP3A	CYP4A
Rat	CYP1A1/2 Ethoxyresorufin O-deethylase	CYP2B1/2 Testosterone 16 β -hydroxylase	CYP2E1 Lauric acid 11-hydroxylase	CYP3A1/2 Testosterone 6 β -hydroxylase	CYP4A1/2 Lauric acid 12-hydroxylase
Mouse	CYP1A1/2 Ethoxyresorufin O-deethylase	CYP2B10 Testosterone 16 β -hydroxylase	CYP2E1 Lauric acid 11-hydroxylase	CYP3A1/2 Testosterone 6 β -hydroxylase	CYP4A10/12/14 Lauric acid 12-hydroxylase
Dog	CYP1A1/2 Ethoxyresorufin O-deethylase	CYP2B11 Testosterone 16 β -hydroxylase		CYP3A1/2 Testosterone 6 β -hydroxylase	
Monkey	CYP1A1/2 Ethoxyresorufin O-deethylase	CYP2B17 Testosterone 16 β -hydroxylase	CYP2E1 Lauric acid 11-hydroxylase	CYP3A8 Testosterone 6 β -hydroxylase	

Protocol

The treatment of animals and harvest of liver samples would be performed elsewhere (in your own laboratory or at another laboratory of your choice), and the frozen tissues would be shipped to Celsis Development Services. Microsomes are prepared from the liver samples and are incubated with CYP-specific substrate, after which CYP enzyme activity, protein concentration, and total CYP content are measured. CYP activities are normalized to mg microsomal protein.

We customize the protocol to meet your specific needs.

References

- 1 Spatzenegger, M.; Jaeger, W. Clinical importance of hepatic cytochrome P450 in drug metabolism. *Drug Metab. Rev.* **1995**, *27*, 397–417.
- 2 Bjornsson, T.D.; Callaghan, J.T.; Einolf, H.J.; Fischer, V.; Gan, L.; Grimm, S.; Kao, J.; King, S.P.; Miwa, G.; Ni, L.; Kumar, G.; McLeod, J.; Obach, R.S.; Roberts, S.; Roe, A.; Shah, A.; Snikeris, F.; Sullivan, J.T.; Tweedie, D.; Vega, J.M.; Walsh, J.; Wrighton, S.A. The conduct of *in vitro* and *in vivo* drug-drug interaction studies: A PhRMA perspective. *Drug Metab. Disp.* **2003**, *31*, 815–832.



1450 South Rolling Road, Baltimore, MD 21227, USA T +1 410 455 1242 F +1 410 455 1245 E customerservice@invitrotech.com