Poster: skin models as alternatives to animal testing

Drug metabolizing enzyme activity in human *in vitro* dermal (EpiDerm™) and airway (EpiAirway™) epithelial models

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Background: Human dermal and airway epithelia contain xenobiotic metabolizing enzymes (XME) including a variety of phase I (oxidative) and phase II (conjugative) activities. These XMEs play an important role in biotransformation of drugs and environmental/occupational chemicals. Biotransformation of chemicals may lead to altered drug activity or formation of toxic/mutagenic metabolites. The present work evaluated expression of XMEs in highly differentiated *in vitro* models of human dermal (EpiDerm™) and airway (EpiAirway™) epithelia that are cultured at the air-liquid interface to facilitate *in vivo*-like chemical exposures.

Materials and Methods: EpiDerm™ and EpiAirway™ cultures were prepared by standard procedures in the MatTek GMP *In Vitro* Model Production Facility. RT-PCR experiments were conducted to evaluate baseline and inducible expression of CYP isoforms in the epithelial cultures. CYP1A1 activty was determined by fluorescence microscopy utilizing ethoxyresorufin as the substrate. Total GST activity in the epithelial models was also evaluated by measuring conjugation of glutathione with 1-chloro-2,4-dinitrobenzene and UDP-Glucuronyltransferase activity was determined by 4-methylumbellipherone conjugation.

Results: In EpiDerm™, CYP1B1, CYP2C19, CYP2D6, CYP3A4 (weak) and CYP3A5 were constitutively expressed. 3-Methylcholanthrene (3MC) strongly increased expression of CYP1A1 and CYP 1B1 in EpiDerm™. EpiAirway™ cultures constitutively expressed CYP1A1 (weak), CYP1B1, CYP2A6, CYP2B6 (weak), CYP2C8 (weak), CYP2C19, CYP2D6, CYP2E1 and CYP3A5, while CYP3A4 and 3A7 were not detected. 3-Methylcholanthrene (3MC) strongly increased expression of CYP1A1 and slightly increased CYP2B6 and CYP2C8 expression in EpiAirway™. Enhanced metabolism of the CYP1A1 and CYP1B1 substrate ethoxyresorufin confirmed increased activity following treatment with 3MC. High baseline GST and UDP-glucuronyltransferase activity in both models was not further enhanced by 3MC treatment.

Discussion: CYP expression in EpiDerm™ and EpiAirway™ showed a high concordance with CYP expression reported for *in vivo* human dermal and airway epithelia. The results demonstrate that the EpiDerm and EpiAirway *in vitro* human epithelial models possess *in vivo*-like XME activities and may thus be useful for evaluating epithelial metabolism of drugs and environmental/occupational chemicals.

Keywords: in vitro skin model