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MEETING ABSTRACTS

HUMAN PRECISION-CUT INTESTINAL SLICES AS A MODEL TO STUDY DRUG-MEDIATED INDUCTION OF INTESTINAL ABCB1 AND CYP3A4

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Drug-mediated induction of the intestinal ABCB1 and CYP3A4 is a clinically relevant phenomenon associated with reduced drug bioavailability. Well-established human models to assess the induction are currently missing, so drug regulatory authorities provide no recommendations to test *in vitro*/*ex vivo* drugs' induction activity. Human precision-cut intestinal slices (hPCIS) contain cells in their natural environment and express physiological levels of nuclear factors required for induction. We recently found that hPCIS incubated for 48 h retained intact morphology, ATP content, and ABCB1 activity. We also confirmed that rifampicin (30 µM) induces gene expression and protein level of the ABCB1 over the 48-h incubation. Here, we aim to evaluate whether model ligands for glucocorticoid receptor (dexamethasone) and vitamin D receptor (vitamin D_3) induce ABCB1 and CYP3A4 expression in hPCIS over the 48-h incubation. Moreover, darunavir, a clinically used anti-HIV drug, was evaluated using this model. Dexamethasone (100 µM) increased the CYP3A4 and ABCB1 gene expression significantly after 48-h, 19.68- and 3.00-fold, respectively. Darunavir (50 µM) after 24-h significantly increased CYP3A4 and ABCB1 gene expression 7.42- and 2.07-fold, respectively. Vitamin D_3 (100 nM) increased CYP3A4 expression 2.29-fold after 48-h incubation; however, confirmation of inducibility requires multiple repeats. On ABCB1 expression, vitamin D_3 had no effect. To conclude, hPCIS is a promising model for investigating drug induction potential. The study was supported by the GAUK 364521 and SVV 260 549.

Keywords: induction; ABCB1; CYP3A4; human precision-cut intestinal slices