Validation of a CYP1A2 and a CYP3A4 Induction Assay Using Puracyp's 1A2-DRE™ and DPX2™ Cell Lines: Comparison Between the Gene-Reporter Assay and Human Hepatocytes Data

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Induction of Cytochrome P_{450} drug metabolizing enzymes (DME) can lead to rapid elimination of APIs resulting in reduced efficacy and increased metabolism which can potentially lead to formation of toxic metabolites. The FDA routinely requests data on induction of human CYP_{450} enzymes CYP1A2 and CYP3A4 by new chemical entities in early development. CYP1A2 expression is regulated via the aryl hydrocarbon receptor (AhR), while CYP3A4 is predominantly regulated via the pregnane X receptor (PXR). Human primary hepatocytes are the preferred in vitro model for studying induction of DME, but their use is limited by unpredictable supply of tissues and interindividual donor variability. In this study, two gene reporter assays for evaluating induction of CYP1A2 and CYP3A4 were validated, using Puracyp's 1A2-DRE™ (a HepG2 derived cell line stably transfected with human AhR gene and a luciferase reporter gene linked to CYP1A2 promoter and the dioxin response element enhancer), and DPX2TM (a HepG2 derived cell line stably transfected with human PXR gene and a luciferase reporter gene linked to the CYP3A4 promoter and enhancer). CYP1A2 inducers β-naphthoflavone, omeprazole, 3-methylcholanthrene (3-MC), and lansoprazole increased CYP1A2 luciferase activity in a concentration dependent manner, resulting in EC_{50} and E_{max} values of 0.56 µM and 30-fold, 9.7 µM and 24.5-fold, 1.9 µM and 27.4-fold, and 3.3 µM and 37.8-fold, respectively. Similarly, CYP3A4 inducers rifampicin, phenobarbital, clotrimazole, erythromycin, and phenytoin increased CYP3A4 luciferase activity resulting in EC_{50} and E_{max} values of 0.85 µM and 7.8-fold, 119.8 µM and 5.0-fold, 0.5 µM and 5.0-fold, 10 µM and 4.2-fold and 17.5 µM and 4.0-fold, respectively. Our reporter gene assay data showed good correlation with data generated using human hepatocytes. Therefore, these validated assays can be used in early development for evaluating induction of CYP1A2 and CYP3A4, providing guidance on compound selection and potential for clinical drug-drug interactions.