Title: Liver-on-chip Model and Application in Predictive Genotoxicity and Mutagenicity of Drugs.

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Abstract:

Currently, there is no test system, whether in vitro or in vivo, capable of examining all endpoints required for genotoxicity evaluation used in pre-clinical drug safety assessment. The objective of this study was to develop a model which could assess all the required endpoints and possesses robust human metabolic activity, that could be used in a streamlined, animal-free manner. Liver-on-chip (LOC) models have intrinsic human metabolic activity that mimics the in vivo environment, making it a preferred test system. For our assay, the LOC was assembled using primary human hepatocytes or HepaRG cells, in a MPS-T12 plate, maintained under microfluidic flow conditions using the PhysioMimix® Microphysiological System (MPS), and co-cultured with human lymphoblastoid (TK6) cells in transwells. This system allows for interaction between two compartments and for the analysis of three different genotoxic endpoints, i.e. DNA strand breaks (comet assay) in hepatocytes, chromosome loss or damage (micronucleus assay) and mutation (Duplex Sequencing) in TK6 cells. Both compartments were treated at 0, 24 and 45 hours with two direct genotoxicants: methyl methanesulfonate (MMS) and ethyl methanesulfonate (EMS), and two genotoxicants requiring metabolic activation: benzo[a]pyrene (B[a]P) and cyclophosphamide (CP). Assessment of cytochrome activity, RNA expression, albumin, urea and lactate dehydrogenase production, demonstrated functional metabolic capacities. Genotoxicity responses were observed for all endpoints with MMS and EMS. Increases in the micronucleus and mutations (MF) frequencies were also observed with CP, and %Tail DNA with B[a]P, indicating the metabolic competency of the test system. CP did not exhibit an increase in the %Tail DNA, which is in line with in vivo data. However, B[a]P did not exhibit an increase in the % micronucleus and MF, which might require an optimization of the test system. In conclusion, this proof-of-principle experiment suggests that LOC-MPS technology is a promising tool for in vitro hazard identification genotoxicants.

Biography:

With her background in biology, specialized in human and animal physiology and toxicology, with 20 years of CRO experience, including 14 years more specifically in applied genetic toxicity testing, Annie has experience directing over than 400 in vitro and in vivo safety genetic toxicology assessment studies. She has high experience in the in vivo assays, the comet assay field, in vitro 3D cell culture models and organ-on-chip microfluidic system. She was responsible of development and implementation of new assays in addition to software validation for automation implementation. She highly cares about animal's welfare by being for long time on the IACUC committee and her interest in innovative methodologies to decrease animal usage. She was also involved in improving current processes and involved in innovation projects as the application of better solutions to regular assays. She currently fills the Scientific Director role of the Genetic Toxicology department at Charles River Laboratories, Senneville site, Canada.