Development of Fit-For-Purpose Multifunctional Liver Co-Culture Systems

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Over the past 3 years, ScitoVation and the ACC LRI have partnered to develop 2D and 3D rat in vitro co-culture models (containing both hepatocytes and non-parenchymal cells) that can be used for safety assessment in lieu of in vivo assays. These co-culture models represent a spectrum of biological and cellular complexity that can be used to determine the effects of compounds on endpoints including cellular viability, proliferation, lipid accumulation, metabolism, and the transcriptome. In light of the Environmental Protection Agency's September 10, 2019 memo committing to the end of mammal in-life testing by 2035, the research aims of this project focus on two of their major initiatives: 1) fit-for-purpose validation to ensure that new alternative methods (NAMs) are equivalent to or better than the animal tests replaced and 2) demonstration that NAMs are applicable for use in risk assessment and that new decision-making approaches are as protective of human health and the environment as existing approaches.

To this end, in 2020 ScitoVation will focus on 1) generating a complete data package to finalize models and to validate the in vitro rat liver cell models as predictive tools for in vivo response to chemical exposure, and 2) design a research plan for development of human 2D and 3D in vitro liver co-culture models.

Implications. Hepatotoxicity is a frequent endpoint leading to the regulation of many chemicals. Since most chemicals are assessed in animal models prior to human exposures, it is important to consider that key species differences between rodents and humans may result in distinct mechanisms of action. Ultimately, the goal of vitro alternatives is to predict human health impacts, but because existing regulatory decisions are principally based on rodent data, our rodent in vitro model that can re-capitulate in vivo responses is valuable for 1) establishing confidence in the alternative approach and 2) early stage testing to reduce or replace in vivo testing.

Collaborations: None.

Key words: hepatocyte, non-parenchymal cell, co-culture, metabolism, 3D models

Current Project start and end dates: January 2020 – December 2020

Peer-reviewed publication(s):

Stefanowicz, A. J., Black, M. B., Beames, T., Andersen, M. E., Clewell, R. A., McMullen, P. D., Hartman, J. K. (2019). Development of 2D organotypic rat liver co-culture models for assessing hepatotoxicant modes of action. Manuscript in preparation.

Presentation(s):

Hartman, J. K., Phillips, M. B. (2018). Designed-for-purpose - complex liver cell cultures for improving in vitro hepatotoxicity testing, Oral Presentation presented at Society of Toxicology 57th Annual Meeting, San Antonio, TX, March 11-15, 2018.

Hartman, J.K., Stefanowicz, A. J., Beames, T. B., Phillips, M. B., Yoon, M., Clewell, R. A. (2018). Development of a multi-functional fit-for-purpose rat liver co-culture assay for hepatotoxicity testing. Poster presented at the Society of Toxicology 57th Annual Meeting, San Antonio, TX, March 11-15, 2018.

Hartman, J. K., Stefanowicz, A.J., Beames, T. B., Roberts, L. A., Slattery, S. (2019). Development of a multi-functional fit-for-purpose rat liver co-culture assay for hepatotoxicity testing. Poster presented at the Society of Toxicology 58th Annual Meeting, Baltimore, MD, March 10-14, 2019.

Other publication(s): None to date.

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