Development of a fit-for-purpose in vitro model of lung toxicity

Artik Mistry, Larry Bowen, Michael Dzierlenga, Marjory Moreau, Patrick McMullen, Melvin Andersen, Jessica Hartman, Scott Slattery. ScitoVation.

The goal of this project is to develop a fit-for-purpose in vitro pulmonary assay that is useful for dose-response studies and chemical risk assessment. Prevalent in vitro approaches employ pulmonary models lacking the complexity needed to model the in vivo lung biology and in vivo exposures, typically using only one cell type with chemical treatments in media. The use of individual cell types does not allow for cell-cell signaling necessary to recapitulate human responses, and media treatments with volatile chemicals or aerosols cannot be easily translated into real-life human exposures. We have developed an improved in vitro assay approach that we believe better represents the human lung and allows for complex air-liquid-interface exposures to various chemical types (gases, vapors, aerosols) using commercially available 3D organotypic co-culture models (e.g., SmallAir-HF (Epithelix) and EpiAirway (MatTek)) and the VitroCell exposure system. We have united these culture and exposure models with assays measuring viability, cytotoxicity, glutathione depletion, epithelial barrier integrity, and transcriptomic changes, and we are validating these approaches for sensitivity and reproducibility. Furthermore, we are investigating the value of the more complex cell culture model and the more complex exposure system compared to simpler approaches using monocultures of immortalized human lung epithelial cell line (BEAS-2B) and/or treatment in media under various testing scenarios. We hypothesize that the complex system will add value when accurate risk assessment is needed or when complex adverse outcome pathways are investigated, but that it may not add value, or could even be counter-productive, for hazard identification scenarios involving acute responses with simple adverse outcome pathways, particularly when high-throughput screening is desirable.

**Implications:** It is imperative for chemical innovators that risk decisions be made using human-relevant models capable of accurately evaluating quantitative dose-response. Our goal is to replace primitive classification and hazard identification methods with methods that support risk-based decisions for safety assessments. High-throughput assays often fail to identify respiratory toxicants due to their volatile nature, and an in vitro cell-based assay would provide significant benefit for chemical safety testing.

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