



DOI: 10.4274/ThoracResPract.2025.s001

Bioengineered Humanoid-on-Chip Platforms: Tools for Evaluating the Effects of Environmental Exposure on Human Physiological Barriers

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INTRODUCTION: Environmental pollutants; bioaerosols, chemicals and micro/nano-plastics (MNPs) can disrupt the mechano-biological processes of the human body, impairing structural, cellular, and molecular functions. Such disruptions may ultimately contribute to the onset of toxicity-associated pharmacokinetic disorders.¹ Traditional *in vivo* and 2D *in vitro* models often fall short in accurately mimicking the complexity of human physiological responses to such environmental exposures. In response, recent advances in microfluidic organ-on-a-chip (OoC) platforms, organoid models, and induced pluripotent stem cell (iPSC) technologies have enabled the development of biomimetic, animal-free, and human-relevant *in vitro* models. These systems increasingly replicate the molecular, structural, and functional characteristics of both healthy² and diseased human tissues, providing powerful tools for toxicological, pharmacological, and pathophysiological research.^{3,4} To further enhance the predictive power of these models, multi-organ integration strategies are gaining attention particularly those emulating organ axis that are functionally and biochemically interconnected.⁵ Among these, the brain-lung-liver-intestine axis represents a critical multi-organ network that mediates systemic responses to external insults. For example, inhaled airborne pollutants can initiate inflammatory signaling in the lung, which may be translocated via the bloodstream to the liver and brain.^{6,7} Similarly, orally ingested MNPs or pharmaceuticals undergo metabolism in the intestine and liver, potentially generating bioactive metabolites that affect the central nervous system (CNS).^{5,8} Such complex inter-organ interactions are essential to understanding the full scope of environmental toxicity and human pathophysiology, yet are poorly captured in isolated organ models.⁵ Bioengineered humanoid-on-chip systems that incorporate the brain-lung-liver-intestine axis within a single fluidically linked microphysiological platform offer a novel solution. These integrated systems can simulate real-time organ-organ crosstalk under dynamic flow conditions, mimicking human circulatory, absorptive, and barrier functions with high fidelity.^{5,6,8} For instance, the intestine-on-chip component can model nutrient or xenobiotic absorption, followed by first-pass metabolism in the liver module,⁸ systemic immune or endocrine responses via the lung module,⁶ and downstream neuroinflammatory

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effects observed in the brain-on-chip compartment.^{5,7} Such systems also allow for the controlled exposure of specific organs to pollutants or therapeutics, enabling precise mechanistic dissection of toxicity pathways across the entire axis.⁹ By combining tissue-specific cellular architectures, mechanical cues (e.g., peristalsis, breathing motions), and physiologically relevant flow dynamics, brain-lung-liver-intestine axis OoC models represent a transformative step toward predictive environmental health assessment.^{5,10} These platforms not only reduce the need for animal testing but also offer scalable, human-relevant alternatives for screening environmental toxins, investigating multi-organ disease mechanisms, and evaluating therapeutic safety and efficacy.^{5,6,7,8,9,10} In an era of rising environmental health concerns, such integrative platforms are poised to play a pivotal role in translational toxicology and precision medicine.⁹

CASE REPORT: Herein, we highlighted our iPSCs or patient-derived brain, lung, liver and intestinal organoid models, iPSCs-differentiated alveolar epithelial cell (AEC) and brain microvascular endothelial cell (BMVEC) barriers, and their OoC models to evaluate the effect of kinds of exposomes. We successfully characterized SPC+ AECs and CD31+ BMVECs with highly transepithelial electrical resistance values as a gold standard, IBA1+ microglia and CD31+ endothelial cells enriched, cortical plate structured advanced matured functional brain organoids, MUC1+ lung-like organoids, EPCAM+/ALB+ liver organoids and human crypt-derived intestinal organoids (Figure 1). Subsequently, we developed integratable organ-specific OoC models utilizing a layer-by-layer fabrication approach to enable co-culture systems of cells and organoids.

CONCLUSION: Our advanced bioengineered models demonstrated that environmental exposures significantly compromised barrier integrity, leading to increased translocation across the tissue construct, reduced cell-organoid viability, and dysregulated expression of inflammatory cytokines and immune cell activity. The resilience of human physiological barriers can be effectively modelled using humanized bioengineering platforms that emulate the dynamic mechanical and biochemical forces present *in vivo*. The integration of organoids, epithelial-endothelial barriers, and OoC technologies that mimics different kinds of organs, holds significant promise as robust and physiologically relevant systems for studying exposure-related responses.

Keywords: Environmental exposure, iPSCs-derived models, organoids, organ-on-chips

ACKNOWLEDGEMENTS: Our studies were supported by the Scientific and Technological Research Council of Türkiye (TUBITAK) through grant numbers 119M578 and 123M406, TUBITAK- Science Fellowships and Grant Programmes (123C325), Türkiye Republic Presidency of Strategy and Budget (2019K12-149080), The Research Fund of Ege University, International Cooperation Project under grant number FUA-2020-22187 and MIT International Science and Technology Initiatives (MISTI) Global Seed Funds project.

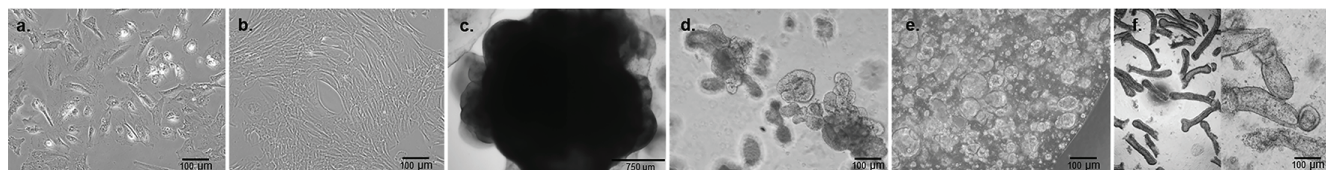


Figure 1. The brightfield images of (a) AECs, (b) BMVECs, (c) brain organoid, (d) lung organoid, (e) liver organoid and (f) intestinal organoid models

AECs: Alveolar epithelial cell, BMVEC: Brain microvascular endothelial cell

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