Development of new therapeutics for pulmonary disorders, and advancement in our understanding of inhalational toxico-pathology have been hindered by challenges to study organ-level complexities of human lung in vitro. Moreover, clinical relevance of widely used animal models of respiratory diseases such as chronic obstructive pulmonary disease (COPD), which poses a huge public health burden, is questionable. Here, we applied a tissue microengineering approach to create a ‘human lung small airway-on-a-chip’ that supports full differentiation of a pseudostratified mucociliary bronchiolar epithelium from normal or diseased donors underlined by a functional microvascular endothelium. Small airway chips lined with COPD epithelia recapitulated features of the disease including selective cytokine hypersecretion, increased neutrophil recruitment, and clinical exacerbations by exposure to pathogens. Using this robust in vitro approach, it was possible to detect synergistic tissue-tissue communication, identify new biomarkers of disease exacerbation, and measure responses to anti-inflammatory compounds that inhibit cytokine-induced recruitment of circulating neutrophils. Importantly, by connecting the small airway chip to a custom-designed electromechanical instrument that ‘breaths’ whole cigarette smoke in and out of the chip microchannels, we successfully recreated smoke-induced oxidative stress, identified unique COPD-specific molecular signatures. Additionally, this platform revealed a subtle ciliary damage triggered by acute exposure to electronic cigarette. Thus, the human small airway-on-a-chip offers a powerful complement to animal models for studying human lung pathophysiology. Moreover, in this presentation, we provide a vision for merger of Organ-on-Chip with emerging technologies such as 3D Bioprinting for tissue and organ engineering, their application for drug discovery and solving pressing societal and public health challenges, and future studies focusing on robust and validated physiologically linked multi-organs on-chip (i.e., virtual human-on-a-chip systems).