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# On The Role of Biomechanics in Respiratory Drug Discovery

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## Extended Abstract

Respiratory diseases represent an enormous health burden and are a leading cause of death worldwide. Yet, the likelihood of a new drug entering the market is very low, <3%. To accelerate drug discovery and testing, there is an urgent need to develop new pre-clinical screening platforms that (1) closely resemble the intact lung both in terms of physiology and biology, (2) are human-based, (3) fast and reliable, and (4) provide physiological biomarkers that can quantify the efficacy of candidate drugs. The human precision cut lung slice (PCLS) is ideally suited to meet these needs. Compared to cell cultures, organoids, and reconstructed tissues, the PCLS retains all resident lung cells, permits fast and direct visualization of cellular and extracellular changes, and can be prepared from disease-bearing lungs. Furthermore, thousands of PCLS can be prepared per human lung and stored via cryopreservation for future use, as needed. To further enhance the utility of PCLS in disease modeling and drug discovery, we have developed several biomechanical systems that can (1) apply mechanical stretch to mimic breathing, mechanical ventilation or coughing, (2) incorporate airway/vascular contraction and relaxation measurements, and (3) provide a macroscale stiffness of the PCLS as well as a microscale stiffness map of the tissue. These biomechanical approaches can be combined with biological and immunological endpoints. Thus, by recreating the biomechanical microenvironment of the intact lung within the PCLS, our technology can be used to probe previously hidden multiscale structure-function-biological relationships during disease progression and drug treatment. To illustrate this, we will present examples from mechanistic studies and drug discovery in pulmonary fibrosis and emphysema, two lung diseases in which the tissue undergoes stiffening and softening, respectively. Our methodologies are generalizable to other organ systems such as the heart, liver, cornea, and skin.