Evaluation of in vitro human alveolar and bronchial microphysiological systems to predict the permeability and absorption of inhaled pulmonary medications.

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Pulmonary therapeutics have an exceptionally poor attrition rate, with only 3% of drugs reaching the market compared to 6-14% of therapeutics for other disease states. The failure to pass clinical trials can largely be explained by the lack of accurate preclinical models available for the lung system. This, together with the extremely high prevalence of lung disease such as COPD, means there is an immediate requirement for better preclinical models to test inhaled medications more rapidly and effectively.

Two microphysiological system (MPS) models representing the human alveoli and bronchi have been developed for this application. The models predict the absorption and permeabilisation of inhaled medications through the lung. The MPS models produce more human-relevant tissues than traditional models through use of perfused media and ALI conditions. Due to an open well insert format, stimuli or compounds can be applied to either side of the insert and multiple volume samples taken for analysis. Together, this allows more precise prediction of human pharmacology.

Here, alveolar epithelial and pulmonary microvascular cells were cocultured in the MPS to assess medications with varying properties. Compounds were applied in small-volume liquid doses to the apical side of the insert and concentrations measured over time in the cell and media samples using LC-MS. The MPS model predictions of drug ADME correlated well with clinical data compared to static and ex vivo data. For example, salbutamol, a short-acting β2 adrenoreceptor agonist, permeated quickly through the tissue and into the basolateral compartment. Compounds with longer lasting clinical effects like fluticasone, a highly lipophilic corticosteroid, were further retained in the epithelial cell compartment. These MPS models will be used to analyse pharmacology and toxicity of inhaled compounds in future studies.