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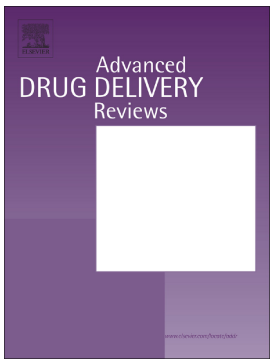

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Engineered cell and tissue models of pulmonary fibrosis

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Abstract: Pulmonary fibrosis includes several lung disorders characterized by scar formation and Idiopathic Pulmonary Fibrosis (IPF) is a particularly severe form of pulmonary fibrosis of unknown etiology with a mean life expectancy of 3 years' post diagnosis. Treatments for IPF are limited to two FDA approved treatments, pirfenidone and nintedanib. Most lead candidate drugs that are identified in pre-clinical animal studies fail in human clinical trials. Thus, there is a need for advanced humanized *in vitro* models of the lung to improve candidate treatments prior to moving to human clinical trials. The development of 3D tissue models has created systems capable of emulating human lung structure, function, and cell and matrix interactions. The specific models accomplish these features and preliminary studies conducted using some of these systems have shown potential for *in vitro* anti-fibrotic drug testing. Further characterization and improvements will enable these tissue models to extend their utility for *in vitro* drug testing, to help identify signaling pathways and mechanisms for new drug targets, and potentially reduce animal models as standard pre-clinical models of study. In the current review, we contrast different *in vitro* models based on increasing dimensionality (2D, 2.5D and 3D), with added focus on contemporary 3D pulmonary models of fibrosis.

Keywords: pulmonary fibrosis; idiopathic pulmonary fibrosis; *in vitro* models; three-dimensional (3D) culture; two-dimensional (2D) culture; two-point-five-dimensional (2.5D) culture; anti-fibrotic drug; hydrogel; decellularized lung matrices; precision cut lung tissue (PCLT); lung spheroid; lung organoid; lung-on-chip

Abbreviations:

3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate (CHAPS); Air-liquid interface (ALI); Alpha-smooth muscle actin (α-SMA); Alveolar type II cells (ATII); American Thoracic Society (ATS); Atomic force microscopy (AFM); Chronic Obstructive Pulmonary Disease (COPD); Clara cell secreting protein (CCSP); Cluster of differentiation-44 (CD44); Cluster of