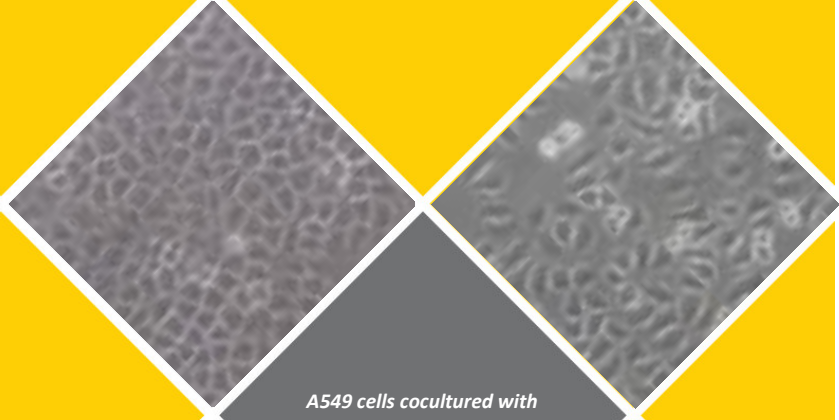
Respiratory Diseases

CHRONIC OBSTRUCTIVE PULMONARY DISEASE



A549 cells cocultured with HLF-1

Background

Chronic obstructive pulmonary disease (COPD) is an umbrella term that is used to describe chronic lung disease and includes the familiar terms of chronic bronchitis, small airways disease and emphysema. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases' (Global Initiative for Chronic Obstructive Lung Disease, 2009). Pathologically the small bronchi (structures 2-4mm in diameter), small airways (<2mm in diameter) and the lower airway lung parenchyma are the main sites in which chronic bronchitis, small airways disease and emphysema develop.

Inhalation of cigarette smoke, occupational and environmental pollutants are the main causes of COPD affect all major compartments of the lung, including the central and peripheral airways, the parenchyma and the pulmonary vasculature.

Smoke exposure can directly injure the lung through the action of toxicants found within smoke but also through the attraction, activation and the release of pro-inflammatory mediators from cells of the immune system. These mediators, which can act locally to damage tissue, can also perpetuate the inflammatory response through the attraction of further inflammatory cells to the site of injury. If the exogenous (cigarette smoke) and endogenous (inflammatory cells) oxidants outweigh the lung's antioxidant capacity, this can lead to injury and further inflammation. Thus, oxidative stress and direct toxicant induced tissue injury drives inflammation and in susceptible individuals drives the disease process and the subsequent development of COPD.

Recent studies have demonstrated that cigarette smoke extract (CSE) is able to inhibit fibroblasts recruitment and proliferation and to alter fibroblast-mediated collagen gel contraction in vitro. Furthermore the cigarette smoke is known to induce epithelial-mesenchymal transition and this transition is likely to be mediated by fibroblasts.

Pathology Model

Initially, 2D coculture of human airway epithelial cells (A549) along with (HLF-1) will be seeded on polycarbonate transwell. The coculture will be exposed to cigarette smoke extract (CSE) in order to evaluate the effect of CLIENT's compound on sigarette smoke lung damage.

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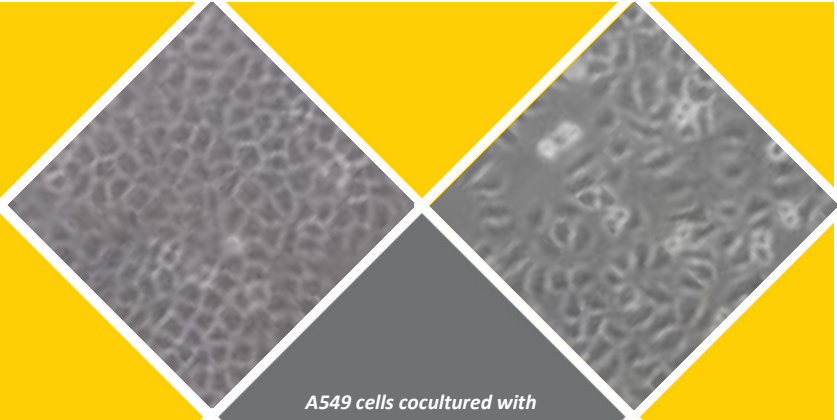

A549 cells cocultured with HLF-1

Readouts

The following parameters will be taken into consideration for 2D model:

- Cell morphology and epithelial integrity (E-cadherin)
- Inflammatory mediator dosage (e.g.: IL-6, IL-8, MMP-1)
- mRNA expression of gene implicated in mucin production (e.g.: MUC1, MUC5, MUC5B)
- Oxidative stress measurement
- Epithelial-mesenchymal transition (a-SMA immunocytochemistry)

The following parameters will be taken into consideration for 3D model:

- Gel contraction assay