Mimicking *In Vivo*-like Physiological Properties of the Human Bronchial Epithelium in *In Vitro* 3-D Cell Cultures

Anna Julia Włodarczyk,[1] Zoë Prytherch,[1] Kati Huttunen,[1,2] and Kelly BéruBé

[1]Cardiff School of Biosciences, Cardiff University, Museum Avenue, Cardiff CF10 3A, Wales, UK
[2] University of Eastern Finland
Presenting author email: wlodarczykaj@cf.ac.uk

The human respiratory muco-ciliary epithelium consists of different cell types, connected by tight junctions; forming a protective barrier against the external environment. The epithelium is attached to a basement membrane through which necessary nutrients are delivered. Apart from a thin layer of mucus, the apical part of the bronchial epithelium is exposed to the ambient air. Mimicking these conditions through the use of 3-dimensional (3-D) filter-well membrane technology, a functional and fully-differentiated muco-ciliary phenotype *in vitro* cell culture model can be obtained. By providing the *in vivo*-like pulmonary microenvironment primary bronchial cells are stimulated to differentiate into a pseudo-stratified epithelium containing, basal, ciliated, Clara, goblet, intermediate and serous cells. In addition to this *in vivo*-like morphology, the cultures attain physiological properties akin to the human bronchial epithelium. Cells form tight junctions, enabling the whole culture to function as a barrier, providing trans-epithelial electrical resistance (TEER). Day 15 of ALI culture conditions results in beating cilia that are fully-grown and spread the mucus produced by the goblet cells. Unlike 'conventional' cell cultures, where tested substances need to be suspended in submerged culture media, our 3-D model of the human bronchial epithelium enables *in vitro* toxicology testing of apically deposited aerosols and/or solubilised substances onto mucus protected cell surfaces. This mimics *in vivo* deposition through inhalation. Moreover, we observe the tissue (i.e. multi-cellular) response, rather than the effect of submerged cell monolayers (i.e. single cell type). The additional protective mechanisms, such as apical mucus, traps inhaled substances and the tight junctions (i.e. barrier function) provide a more *in vivo*-like response when compared to submerged monolayer cultures. Our 3-D model of the human bronchial epithelium maintains the *in vivo* complexity observed in the *in-situ* human lung and is a reliable *in vitro* tool that can be employed to obtain robust predictive *in vivo* responses for human endpoint data.

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