When lipid nanoparticles meet lung surfactant: a comprehensive study of their potential for inhaled therapeutic applications

Gloria Gómez-Montesino [1], José Carlos García-Perdiguero [2], Miguel Manzano [2,3,4], María Vallet-Regí [2,3,4], Alberto Hidalgo [5], Otmar Schmid [5], Jesús Pérez-Gil [1,3], Olga Cañadas [1,3]

[1] Department of Biochemistry and Molecular Biology, Faculty of Biological Sciences, Complutense University, Madrid, Spain [2] Department of Chemistry in Pharmaceutical Sciences, School of Pharmacy, Complutense University, Madrid, Spain. [3] Research Institute "Hospital Doce de Octubre (imas12)", Madrid, Spain. [4] Networking Research Center on Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN), Madrid, Spain. [5] Institute of Lung Health and Immunity (LHI), Helmholtz Munich, Comprehensive Pneumology Center (CPC-M), Member of the German Center for Lung Research (DZL), 85764 Neuherberg/Munich, Germany.

glgomez@ucm.es

Lung surfactant (LS) is a lipid-protein complex system that stabilizes the respiratory air–liquid interface by reducing surface tension and thus facilitating breathing dynamics. Furthermore, LS has also been proposed as a potential carrier to transport inhaled therapeutics over the respiratory interface, known as interfacial delivery. However, its ability to effectively transport nanomaterials over the mentioned interface is still not completely understood.

In this work, we studied the interfacial pulmonary transport of lipid nanoparticles (LNPs), which are often used for drug delivery, in the presence of LS using biomimetic *in vitro* models. To do so, we combined a double Langmuir surface balance and a custom-built interfacial delivery device to quantify transport of LNPs across a continuous air-liquid interface under both static conditions and breathing-like compression-expansion dynamics. Physicochemical stability of LNPs at 4 °C and 25 °C was assayed under storage-relevant conditions. In parallel, cargo release kinetics were studied both in the absence and presence of LS. The absence of surfactant was aimed at measuring intrinsic nanoparticle stability, while the presence of LS allowed us to evaluate cargo release in a controlled manner under conditions that better mimic the pulmonary context. Additionally, the impact of LNPs on LS biophysical performance was assessed using a Captive Bubble Surfactometer. Finally, preliminary experiments in alveolar A549 epithelial cells and THP-1-derived macrophages are currently ongoing to evaluate nanoparticle uptake, cytotoxicity, and inflammatory responses, including metabolic activity (MTT assay) and IL-6/IL-8 secretion.

Overall, these experiments provide a more comprehensive picture of how suitable LNPs are for interfacial delivery, helping to clarify the strengths and weaknesses of LNPs as platform for inhaled drug delivery.

Keywords:
Lipid nanoparticles (LNPs); Lung surfactant; Air–liquid interfaces; Interfacial delivery; Nanoparticle–interface interactions.