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Mimicking Homeostasis between Bacteria, Bacteriophages and Airway Epithelial Cells *In Vitro* for Microfluidic Applications

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Bacteriophages (or simply phages) represent the most extensive group of viruses within the human virome and have a significant impact on general health and well-being by regulating bacterial population dynamics. *Staphylococcus aureus* is an opportunistic pathogen that colonizes the anterior nostrils, pharynx and skin and can cause upper respiratory tract infections that can spread to the lower airways. This study was conducted as part of the EU-funded programme CURE: "Constructing a Eubiosis Reinstatement Therapy for Asthma" (https://cordis.europa.eu/project/id/767015), which aims to unravel the role of phages as novel therapeutic modalities for asthma. We have developed a human cell-based homeostasis model between a clinically isolated strain of *S. aureus* 141 and active phages for this strain (PYO^{Sa141}) isolated from the commercial Pyophage cocktail (PYO). The cocktail is produced by Eliava BioPreparations Ltd (Tbilisi, Georgia) and is used as an add-on therapy for bacterial infections, mainly in Georgia. The triptych interaction model was evaluated by time-dependent analysis of cell death and inflammatory response of nasal and bronchial epithelial cells. Inflammatory mediators (IL-8, CCL5/RANTES, IL-6 and IL-1β) in the culture supernatants were measured by enzyme immunoassay and cell viability was determined by crystal violet staining. By measuring trans-epithelial electrical resistance, we assessed the epithelial integrity of nasal cells that had differentiated at air-liquid interface cultures and under static or constant flow conditions. PYO^{Sa141} was found to have a prophylactic effect on airway epithelial cells exposed to *S. aureus* 141 by effectively down-regulating bacterial-induced inflammation, cell death and epithelial barrier disruption in a time-dependent manner. Overall, the proposed model represents an advance in the way multi-component biological systems can be simulated *in vitro* and is currently being further evaluated using an in-house fabricated microfluidic device.