

## Inhalable nanoparticles for antimicrobial peptide delivery in lung infections

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The pulmonary administration of antimicrobial peptides (AMPs) represents a promising alternative to conventional antibiotics for the treatment of multi-drug resistant (MDR) lung infections. However, their *in vivo* efficacy is often limited by physiological and pathological barriers, such as the airway mucus and, in infectious conditions, the bacterial biofilm. These barriers significantly hinder the diffusion, retention, and activity of AMPs at the infection site, posing challenges for their clinical application.

To address these limits, we investigated the development of biodegradable polymeric nanocarriers based on poly(lactide-co-glycolide) (PLGA) for the pulmonary delivery of AMPs. Various AMP candidates, including colistin [1], SET-M33 [2], and Esculentin [3,4], were tested. All formulations were engineered using surface-modified PLGA nanoparticles to modulate their interaction with airway barriers. Surface engineering strategies included stabilizers and coatings such as polyvinyl alcohol (PVA), polyethylene glycol (PEG), chitosan, and poloxamers (F127 or F68), selected for their ability to influence drug release, mucopenetration, and biofilm diffusion.

Surface modification emerged as a critical factor in tuning the interaction of nanoparticles with biological barriers. The use of biocompatible polymers to engineer the nanoparticle surface allows for the modulation of properties such as mucoadhesion or mucus penetration, which are essential to promote efficient diffusion through the mucus and biofilm layers. These strategies are particularly relevant in pulmonary delivery, where overcoming these barriers can enhance drug localization, prolong residence time, and ultimately improve therapeutic efficacy of antimicrobial peptides.

The obtained findings highlight the potential of rationally designed PLGA-based nanocarriers with tailored surface properties to improve the pulmonary delivery of antimicrobial peptides and overcome biological barriers associated with chronic lung infections.

- [1] d'Angelo I, Casciaro B, Miro A, Quaglia F, Mangoni ML, Ungaro F. *Colloids and Surfaces B: Biointerfaces* 135 (2015) 717–725.
- [2] Cresti L, Conte G, Cappello G, Brunetti J, Falciani C, Bracci L, Quaglia F, Ungaro F, d'Angelo I\*, Pini A. *Pharmaceutics* 15 (2023), 3.
- [3] Casciaro B, d'Angelo I, Zhang X, Loffredo MR, Conte G, Cappiello F, Quaglia F, Di YP, Ungaro F, Mangoni ML. *Biomacromolecules*. 13 (2019);20(5):1876-1888.
- [4] Cappiello F, Casciaro B, Loffredo MR, Puglisi E, Lin Q, Yang D, Conte G, d'Angelo I, Ungaro F, Ferrera L, Barbieri R, Cresti L, Pini A, Di YP, Mangoni ML. *Pharmaceutics* 14 (2022), 2297.