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Inhalable dry powders for chemically-modified human Cationic AntiMicrobial Peptides (CAMPs): moving toward in vivo application

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Background. The diffusion of multidrug resistant (MDR) bacteria has highlighted the need of new antibiotics, but, so far, progress in developing them has been slow. Cationic Antimicrobial Peptides (CAMPs) are the first line of defense of multicellular eukaryotics against microbial invasions. Even if the protein nature of CAMPs makes difficult their use as systemic antimicrobials they are ideally suited for direct delivery to airways and lung.

Hypothesis and objectives. The main aim of this project is to develop inhalable dry powders for lung-delivery of CAMPs and CAMP-releasing proteins (CAMP-RPs) carrying simple chemical modifications which improve their antimicrobial activity.

Methods. Using Methods. developed in our laboratory we prepared three modified human CAMP-RP, lysozyme (mhLYS), RNase 5 and β-defensin-1 active on E. coli, P. aeruginosa and S. aureus.
By spray drying we prepared inhalable dry powders containing mhLYS and carriers already approved in inhaled medicines. As an alternative tool we also developed inhalable dry powders containing biodegradable nanoparticles (Nano-Embedded Microparticles, NEM).

Results. Intra-tracheal administration to mice by the Penn Century MicroSprayer® Aerosolizer of rhodamine-labeled mhLYS showed that the distribution among lung lobes was asymmetric (rhodamine was always found only in 1 or 2 lobes of the right lung) and heterogeneous suggesting that a poor distribution may have contributed to low safety and efficacy showed by CAMP-RPs. We developed powders optimized for the release of mhLYS into the lung. In particular, mannitol/CAMP-RP powders showed good aerosolization properties and complete recovery of the antimicrobial activity. Moreover, we produced NEM whose properties are well suited for the direct administration to bronchi/bronchioles of colistin, a model CAMP. Mannitol/labeled-mhLYS powers were administrated intratracheally to mice by the Penn Century Dry Powder Insufflator™. Similarly to the results obtained using the aerosolizer, the distribution of the fluorescently-labeled CAMP-RP in lung lobes was asymmetric and heterogeneous. Again rhodamine was found prevalently in the lobes of the right lung. Our results suggest that intra-tracheal administration of powders in mice requires further improvement before it is possible to perform a reliable efficacy test in vivo.

Spin-off for research & clinical purposes. In perspective, our inhalable powder formulations may be a valuable support tool for the treatment of CF. Our results are a further step toward the development of CAMP(-RP)-based pharmacological formulations.

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