Smart nano into micro tools for pulmonary therapy of cystic fibrosis

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Cystic fibrosis (CF) is a lethal autosomal recessive disease triggered by mutations in the gene encoding the CF transmembrane conductance regulator protein (CFTR). The airways of CF patients are plugged with mucopurulent secretions containing abundant bacteria and neutrophils, and death results from progressive destruction of the lungs [1]. Newly introduced therapies have resulted in great improvements in length and quality of life. However, intermittent pulmonary exacerbations or acute worsening of infection and obstruction require more intensive and aggressive therapies. Inhalation of tobramycin is extensively used in patients with CF as a first-line treatment for the eradication of *Pseudomonas aeruginosa*, which causes an acceleration of the decline in lung function [2]. However, the efficacy of tobramycin is still limited by the inability to achieve sufficient levels at the site of infection, caused by a poor mucus penetration and to the inactivation of the drug through binding with mucus components [3]. For this reason, in our laboratory, a nanometric ion pair complex, prepared between tobramycin, positively charged, and a biocompatible synthetic polyanion, named PHEA-EDA-GlucA, was encapsulated into a *Nano into Micro* (*NiM*) formulation, inhalable as dry powder. It has been demonstrated that the ion pair complex alone is able to achieve a controlled tobramycin release and to exercise a pronounced antimicrobial activity against *P.aeruginosa* pathogen; moreover, the resulting *NiMs* are also able to modify the rheological properties of a CF-Artificial Mucus (CF-AM), facilitating the drug diffusion through it, thanks to mannitol ability to change the viscoelastic properties of mucus, increase the hydration of the periciliary fluid layer and mucus clearance of the retained secretions.

The potential of this strategy wasimproved by adding special “helping materials”, such as N-acetylcysteine, L-arginine or cysteamine, having each one a specific action in the improvement of pulmonary function in CF patients. The advantage of these formulations is due to the dual antimicrobial and mucus viscosity-reducing effect, absent in TOBI®Podhaler®, the only one commercial available dry powder formulation of tobramycin, that increases mucus viscosity and allows a slower tobramycin release.

In 2012 the most important medicine agencies have approved the first drug treating the defect of CF, ivacaftor (Kalydeco®), that is a CFTR-potentiator that stabilizes the open state of CFTR, thus increasing channel opening time.

In order to increase the drug concentration at the site of disease and to achieve a sustained drug delivery, potentially improving the therapeutic efficacy and reducing systemic side effects, ivacaftor was entrapped into mucus-penetrating polymeric nanoparticles (NPs). Fluorescent NPs, based on a mixture of two synthetic amphiphilic polymer, mamed PHEA-RhB-PLA-PEG and PHEA-PLA-Tat, showed mucus-penetrating ability and enhanced lung cellular uptake in presence of CF-AM. Moreover, pulmonary drug delivery systems composed by mucus-penetrating NPs loaded with ivacaftor, inhalable by dry powder inhalers (DPI) devices, were obtained by using the *Nano into Micro* strategy and realized by spray-drying mannitol (Man) or its mixture with cysteamine (Cyst). Spherical *NiMs* with suitable dimensions for an optimal lung deposition were produced, showed high entrapment efficiency values and provided an optimal preservation and stabilization of NPs technological and fluorescence properties. The resulting *NiMs* are, also in this case, able to modify the rheological properties of a CF-AM, facilitating drug diffusion through it, thanks to Man and Cyst ability to change the viscoelastic properties of mucus.

Thus, *Nano into Micro* strategy represents a promising approach to deliver innovative and convenient drug delivery systems based on NPs or ion pair complex, whose administration by nebulization is not feasible or convenient. *NiMs* could be administered to the lungs by using DPI devices, characterized by faster delivery, ease of use, portability, reduced need for cleaning and room temperature storage, improved treatment compliance and better therapeutic outcomes for CF patients.

References

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