Novel nanoparticle-based therapy to eradicate *Pseudomonas aeruginosa* infections in cystic fibrosis lungs: dual drug release by cubosomes

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Cystic fibrosis (CF) is a genetic disease that origins a defective chloride secretion resulting in the accumulation of thick and sticky sputum in lungs. The accumulated sputum is rich in nutrients being, thus, a good environment for microbial colonization. *Pseudomonas aeruginosa* have a significant prevalence among CF patients and its presence is highly associated with poor lung function and mortality of patients [1]. Numerous antibiotic strategies have been used varying in route of drug administration (systemic, oral, inhaled or route combination), classes of antibiotics and treatment duration in attempt to eradicate *P. aeruginosa* infections. Despite the long and aggressive antibiotic treatments using more than one antibiotic simultaneously, *P. aeruginosa* still persists causing chronic infections virtually impossible to eradicate [2]. Our recent data demonstrated that the failure of the current antibiotic treatments contributes to the emergence of multidrug resistant (MDR) *P. aeruginosa* compromising, thus, the second therapeutic line, which is quite alarming. According the same study, our results pointed out that antibiotic failure could be caused by the sub-optimal concentration that achieved bacteria. CF features such as extracellular DNA, mucin, pH, limited oxygen availability and biofilm formation can neutralize or diminish the concentration during antibiotic penetration into CF mesh.

The absence of new antibiotic molecules and the spread of MDR *P. aeruginosa* prompted us to search for innovative therapeutic strategies effective against *P. aeruginosa*. Nanoparticles (NP) exhibited exceptional properties for drug delivery with excellent pharmacokinetics profiles because it ensures deposition of the drug at the infection site with higher local drug availability using reduced dosages and avoiding systemic toxicity. NP such as liposomes, polymeric and lipid NPs have been explored for pulmonary delivery of antibiotics with promising results. The novelty of this study lays on the use of a NP poorly explored, the cubosomes, and novel synergic antimicrobial combinations, exploring anti-virulence agents and antimicrobial peptides with traditional antibiotics. Cubosomes can constitute a powerful and innovative delivery vehicle of antimicrobials for CF treatment due to the possibility of combining antimicrobials with different water solubilities that can display synergistic effects and combination of controllable release profiles.

To accomplish this purpose CEB and INL started working together. INL has been preparing the first set of cubosomes with selected antimicrobial agents, which will then be tested at CEB against *P. aeruginosa* bacteria grown in simulated CF environment.

References

[1] Cystic Fibrosis Foundation, Patient Registry 2015 annual report. Bethesda, Maryland: Cystic Fibrosis Foundation, 2015

[2] Sousa AM, Pereira MO Pseudomonas aeruginosa Diversification during Infection Development in Cystic Fibrosis Lungs - a review. Pathogens 3: 680-703, 2014