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Anti-virulence therapy against *Pseudomonas aeruginosa*: identification of antibiofilm drugs and development of inhalable Niclosamide and Flucytosine formulations

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Background. Early aggressive and maintenance antibiotic therapies prolong cystic fibrosis (CF) patient life, but are not able to eradicate Pseudomonas aeruginosa lung infection. Anti-virulence drugs represent a promising therapeutic option in CF. These drugs could alleviate the severity of the infection, reduce lung inflammation, and help antibiotics in eradicating the P. aeruginosa infection. The long times and high costs required for the development of "brand new" anti-virulence drugs can be saved by repurposing "old" drugs already used in humans for different diseases. We have recently shown that the antimycotic drug flucytosine and the anthelmintic drug niclosamide can be repurposed to suppress P. aeruginosa virulence in vitro and in animal models of infection. However, the old drugs need to be re-formulated for the new application in CF therapy.

Hypothesis and objectives. 1) To develop and validate inhalable formulations of flucytosine and niclosamide for CF therapy.
2) To discovery additional drugs with anti-virulence activity against P. aeruginosa.

Essential Methods. Inhalable formulations of flucytosine and niclosamide have been developed through the adequate combination of available technologies and excipients for inhaled drugs and characterized in vitro and in vivo for their activity and toxicity.
Bioluminescent-based biosensors targeting the GacS-GacA system and the c-di-GMP system of P. aeruginosa, crucial for biofilm development, have been used for the screening of 1600 "old" drugs.

Results. 1) Flucytosine and niclosamide inhalable formulations have been successfully developed. These formulations are: i) active against P. aeruginosa strains isolated from CF patients; ii) easily delivered through advanced nebulizers and breath-actuated dry powder inhalers available to CF patients for drug inhalation; iii) display low toxicity in vitro and in animal models. Flucytosine administered as inhalable liquid formulation is active in protecting mice from the P. aeruginosa lung infection. Further experiments in animal models of infection aimed at testing the developed flucytosine dry powder for inhalation and the inhalable niclosamide liquid formulation are in progress.
2) The screening with the biosensors described above gave no promising results.

Spin-off for research & clinical purposes. 1) The efficacy of flucytosine and niclosamide formulations needs to be confirmed by the on going studies in animal infection models before starting phase I clinical trials.

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