Tackling phage resistance to increase the robustness of phage therapy for curing *Pseudomonas aeruginosa* infections in patients with Cystic fibrosis

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General data

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Abstract text

Abstract text: Patients with Cystic Fibrosis (CF) are highly susceptible to lung infections caused by different bacteria, among which *Pseudomonas aeruginosa* (Pa). Phage therapy, namely exploiting phages (bacteria-specific viruses) to kill infecting bacteria, represents a promising strategy for curing bacterial infections refractory to antibiotics in these patients. We assembled a collection of phages able to kill Pa clinical strains isolated from patients with CF and developed a four-phage cocktail (CK4) able to treat Pa infections in animal models among which a *cftr*-loss-of-function zebrafish. However, the success of phage therapy may be endangered by the emergence of mutant bacteria resistant to phages. Addressing this challenge constitutes the focal point of our research. In a previous work, we found that CK4-resistant mutants are easily isolated from cultures of the susceptible PAO1 strain grown in either a standard laboratory medium or an artificial sputum medium mimicking the composition of the airway fluid of people with CF. In both cases, CK4 resistant mutants are defective in lipopolysaccharide (LPS) biosynthesis, suggesting that all CK4 components exploit the LPS as receptor for adsorption. Indeed, all phages that we have collected so far from environmental samples rely on either LPS or type IV pilus (T4P) as receptors. Heterogeneity of LPS and lack of pili may explain the widespread phage-resistance shown by Pa clinical strains isolated from CF patients. This makes of pivotal importance the identification and/or construction of phages using different receptors that may make the therapy more robust towards resistance. We have found and are currently characterizing six new natural phages, some of which grow on multi-phage resistant or even pan-resistant strains isolated form people with CF. Overall, our data show that natural Pa phages not relying on LPS or T4P for adsorption are relatively rare. Moreover, we have implemented a mutagenesis approach to derive phages with altered host range building upon already characterized phages potentially applicable to therapy. The preliminary results of this approach will be presented. Finally, we are testing whether the treatment with Trikafta may select bacteria with altered phage-susceptibility profile. The results we have obtained so far show no correlation between the treatment with Trikafta and phage resistance degree.

Conflict of interest

Conflict of interest: **I confirm there is no conflict of interest** relative to my submitted abstract.

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