BACTERIOPHAGES AS WEAPONS TO FIGHT INFECTIONS CAUSED BY ANTIBIOTIC-RESISTANT BACTERIA

PhD Student: Greta Ponsecchi / *Supervisor*: Prof. Marco Maria D'Andrea

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Following the introduction of the first antibiotic into clinical practice in the 1940s, the treatment and prevention of infectious diseases changed and improved radically. However, the efficacy of the different antibiotics used for the treatment of infectious diseases was soon compromised by the emergence and spread of resistant bacteria. Indeed, due to the increasing selective pressure induced by the use of antimicrobial agents, bacteria evolved resistance mechanisms that allowed them to survive, persist and spread in the environment despite the presence of antibiotics. Today, due to the paucity of effective antibiotic molecules, the slow development of new antimicrobial agents, and the parallel massive spread of multidrug-resistant (MDR) or pandrug-resistant (PDR) bacteria, mankind is in a critical situation and faces the risk to return back to a "pre-antibiotic era". Antibiotic resistance is therefore one of the major threats of modern medicine, with dramatic implications for global health in terms of mortality and morbidity, especially considering immunocompromised individuals.

Consequently, this emergency requires the study and development of new therapeutic approaches that could complement or replace the conventional antibiotics. In recent years, the so-called 'phage therapy', i.e., the use of lytic bacteriophages (or phages), or components thereof, that are able to selectively attack bacterial cells with the aim of eradicating the infection, has been re-evaluated. In comparison with antibiotic therapy, the use of bacteriophages has several advantages, the most important of which is the ability to attack MDR bacteria selectively and effectively, independently of their antibiotic resistance. Moreover, given the fact that infections by MDR bacteria are often sustained by a restricted number of clonal groups, the approach with phages could represent a tool of "high precision medicine" able to target just the pathogen with a very high selectivity.

In this regard, the main aim of my PhD project is to search and deeply characterise specific lytic bacteriophages targeting bacterial clones implicated in severe healthcare-associated infections. It is expected to select phages against I) MDR strains of *Klebsiella pneumoniae* in particular belonging to the clonal group ST147, ST307, ST395, and ST405, which are endemic in Italy and in several other international settings; II) XDR strains of *Pseudomonas aeruginosa* belonging to high-risk clones commonly associated to severe infections at a global scale (e.g., ST111, ST175, ST235, and ST621) and III) strains of *Mycobacterium abscessus* subsp *abscessus* cluster 1 and cluster 2, which are frequently associated with severe chronic infections in patients with cystic fibrosis. Other bacterial targets will be possibly selected during the PhD period on the basis of the evolving epidemiological scenario.