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Overview. Phage therapy is considered theoretically as alternative to overcome antibiotic resistance and various studies show that phage therapy has been used clinically and has been effective. Unfortunately, the outcome of phage treatments is unpredictable due to factors such as the type of phage, the type of target bacterium, the location of the infection in the body, and the lifestyle of the target bacteria whether planktonic or in biofilms. More importantly, the collateral effects of phage resistance are unknown, especially those concerning the appearance of phage resistant bacteria upon therapy. Whether phage-resistant bacteria display enhanced virulence, increased antibiotic tolerance and resistance, entry to dormancy or persister states have not been systematically explored. These knowledge gaps depend in part of single-minded approaches. Typically, phage-specific research focuses on the phage biology and genetics, while phage therapy research focuses on the delivery/efficiency of phage particles. In these contexts, the relationship between phage resistance and pathogenicity is completely ignored. We propose to bridge this gap by developing an interdisciplinary approach to understand phage biology in the context of the consequences of phage resistance and the behaviour of resistant bacteria.
We will test in this proposal the hypothesis phage-resistant bacteria are less virulent and more susceptible to host clearance mechanisms by immune system. Most phages target bacterial surface molecules, especially those of carbohydrate nature, which are the dominant phage receptors. Surface carbohydrates and glycoconjugates such as capsules and lipopolysaccharide (LPS) serve as molecular patterns for recognition by the innate immune system, and also provide shields to antibiotic entry and host defence mechanisms (e.g. complement system and phagocytosis). Loss or alteration of these molecules by gene mutation, which leads to phage resistance, could result in more susceptible bacteria. Therefore, we propose to apply a multidisciplinary approach to evaluate the changes in surface glycans of phage-resistant bacteria and characterize these strains in term of their genome analysis, pathogenicity, interactions will the innate immune system, antibiotic resistance, and biofilm formation. For this, we will blend three world-class research groups. The Wroclaw group led by Prof Drulis-Kawa has demonstrated expertise in phage biology, phage genomics and genetics, and also in the biochemical characterization of phage enzymes interacting with bacterial surface glycans. The group led by Prof Valvano at Queen's University Belfast in internationally recognized for research in the pathogenicity of opportunistic bacteria, macrophage-bacteria interactions, LPS biochemistry, and resistance to antimicrobial peptides. The Prof Molinaro group at the University of Naples brings world-class expertise in glycochemistry, structural characterization of bacterial glycans and interactions of glycans with glycan-specific enzymes using sophisticated tools like nuclear magnetic resonance.

Significance. Concerning significance, our proposal will help understand the balance between phage as a population control agent vs. phage as an eradication agent. It will also provide a mechanistic view on why phage therapy can work, not necessarily by eradiation of sensitive bacteria, but rather from the modification of the bacterial population where phage resistant mutants become more susceptible to treatment and host clearance.