

Parasites, broadly defined as organisms that live at the expense of other organisms, constitute almost half of all known species on earth. From an evolutionary point of view, their survival depends on the ability to access their resource – the hosts. Hence parasites constantly evolve novel weapons to infect their hosts, while hosts constantly evolve novel weapons to resist their parasites. This arms race, known as antagonistic co-evolution, can over time lead to diversification of such weapons and defences and is an important process in generating biodiversity on Earth.

One great model system are bacteria and their viruses – called (bacterio)phages. Like other parasites, phages depend on their hosts (bacteria) to reproduce, hence to survive they need to be able to infect bacteria. Bacteria are thus under selective pressure to escape the phage predation, while phages are under selective pressure to catch up. Numerous experimental studies have demonstrated that these dynamics can accelerate bacterial evolution and even affect the structure of entire bacterial populations. On the other hand, we know that phages can play an important role in horizontal transfer of genes that help bacteria survive in new environments, for example by helping them become resistant to antibiotics. Nevertheless, we do not quite fully understand how co-evolution with phages affects the evolution of clinically-relevant bacteria. This is important because some bacterial pathogens that are known for causing opportunistic infections that do not respond to antibiotic treatment are evolving rapidly. Knowing how their parasites – phages – contribute to their evolution could help us better predict clinical evolution and potentially design better and smarter treatments against bacterial infections.

This proposal will help address this knowledge gap by studying a bacterial species called *Klebsiella pneumoniae* and its phages. Specifically we will focus on interactions between bacterial surface sugars that phages often use as receptors to attach to the bacterium before proceeding with an infection. To do this, our team will use a combination of cutting-edge biotechnology, including bioinformatics, genomics and experimental microbiology. The proposal has three main goals. First, using thousands of genomes of *Klebsiella* bacteria from epidemiological collections, we will use bioinformatics and computer simulations to study how bacterial surface molecules and prophages change over time, and identify molecules that phages use to "enter" the bacterial cell. Second, we will use experiments to isolate these proteins and check which surface molecules they recognise. Finally, we will combine the two approaches to understand whether we can predict which phages infect which surface molecules using just bioinformatics and understand their spread throughout bacterial populations.

Why is this research important? *Klebsiella* bacteria are one of the most common causes of multidrug-resistant infections in hospitals and we are currently in need of new weapons against them. One solution is to study phages which, over the course of millions of years of co-evolution, have invented many such weapons that remain unknown to us. Our research, by investigating previously unknown phages, can provide us with many new ideas for biotechnological tools against infectious bacteria. Second, specific bacterial sugars, called serotypes, are often target of vaccines that protect against bacterial diseases. By understanding the diversification of these sugars, we can help design better vaccine targets and predict new serotypes to be included in future vaccines. Finally, phages are sometimes being used as a last resource against bacterial infections. Thanks to this research we will get a better understanding of which clinical lineages could be potentially targeted by phages if these approaches become more common.