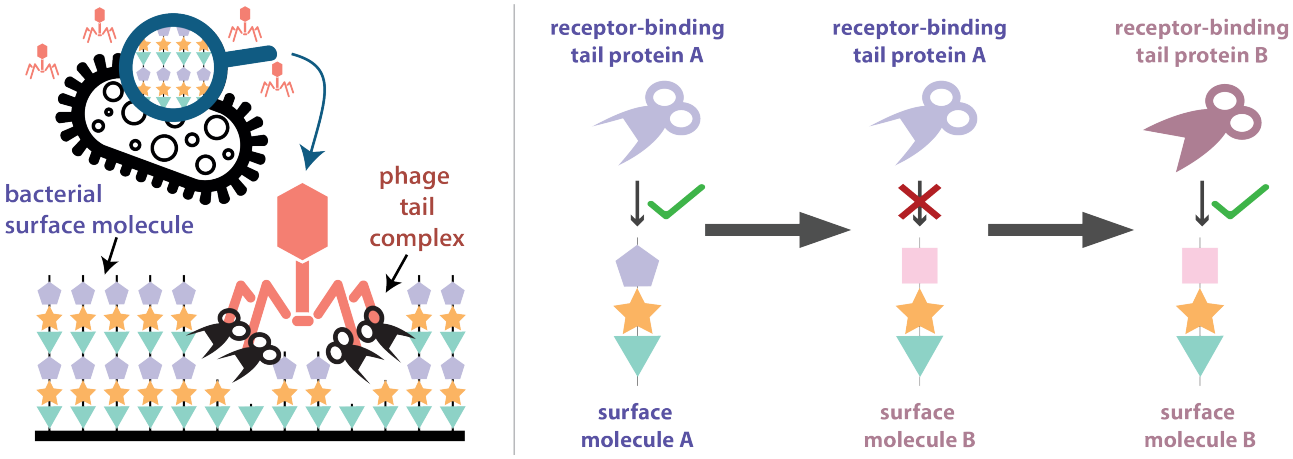
Parasites, broadly defined as organisms that live at the expense of other organisms, constitute almost half of all known species on earth. From an evolutionary point of view, their survival depends on the ability to access their resource – the hosts. Hence parasites constantly evolve novel weapons to 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 phages. Bacteria are surrounded by a plethora of surface molecules (like capsules, proteins or LPS), and phages often use these molecules as receptors to attach to the bacterium before proceeding with infection using their tails (see Figure below). Experiments have shown that bacteria often modify these molecules to escape the infection by the phage and that phages can modify their tail proteins to catch up with evolving bacteria. Furthermore, we know from studying different bacterial species that genes that encode for bacterial surface molecules are some of the most diverse and fastest evolving in bacterial genomes. Nevertheless, there is still a lot we do not really understand about the co-evolutionary process, for example whether phage proteins that interact with bacterial surface molecules also evolve faster than other proteins, as it is the case in bacteria.



(Left) Bacterial surface molecules are often used by their viruses, phages, as receptors to start an infection. To this end, they have highly specialised receptor-binding proteins. (Right) Bacteria can modify the molecules to escape the phage and phages can in turn modify their receptor-binding proteins to catch up with bacteria. While this process can in theory drive the diversity of both molecules, there is still a lot we don not understand about it. It is important to do so as these interactions form the basis of some current and future approaches against multi-drug resistant bacteria (eg, next generation antimicrobials).

This proposal will help address this knowledge gap by studying a bacterial species called *Klebsiella pneumoniae* and its phages. To do this, our team will use a combination of cutting-edge biotechnology, including bioinformatics, genomics, microbiology and structural biology. The proposal has three main goals. First, we will sample thousands of genomes of phages that infect bacteria of *Klebsiella* by scavenging phages that integrate into bacterial genomes (and thus have already been sequenced within bacterial genomes but have not been extracted). Second, we will characterise phage tail and non-tail proteins by using latest bioinformatic tools to compare distant protein families and learn about their functions. Third, we quantify the speed of evolution in different phage protein families, comparing whether tails evolve faster than non-tails.

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, but the idea of using live viruses as drug has been controversial as bacteria and viruses co-evolve. Hence, there is a need for fundamental research to elucidate the co-evolutionary dynamics underlying bacterial-phage interactions to make evidence-based statements about the future of phage therapy.