The most intense co-evolution and arms race on our globe take place between bacteria and their viruses, called bacteriophages. (Bacterio)phages recognize and kill their bacterial host with very high specificity. Every phage infection is initiated by the recognition of a specific structure on the surface of the bacterium (called receptor) by a so-called receptor-binding protein (RBP) protruding from the phage particle. Some phages recognize and infect only one type of bacterial host, while others can attack different bacterial hosts using different RBPs. An interesting example is jumbo phages infecting *Klebsiella* species, which have a very large genome and are equipped with multiple RBPs assembled in a flower-like structure. Consequently, jumbo phages can infect multiple strains of *Klebsiella* species making them very appealing from a therapeutic point of view. Phage therapy is a long-known concept, but only recently regaining high interest. Phages are then used to treat multidrug-resistant (MDR) bacterial infections instead or as a complement to antibiotics. Since the mortality rate due to MDR *Klebsiella pneumoniae* infections with no traditional therapeutic option is drastically increasing, the World Health Organization marked this bacterium as a Priority 1 (critical) pathogen. Therefore, finding alternative, effective therapies is of utmost importance.

The *Klebsiella* cell is covered with a capsule composed of polysaccharides giving more than eighty different capsular types. Not surprisingly, the capsule located on the bacterial surface is the major phage receptor that is targeted, recognized, and digested by RBPs enabling the adsorption and further propagation of *Klebsiella* virus. The capsule is also the most important virulence factor of *Klebsiella*, utilized to escape the human immune system response.

Most jumbo phages have been discovered only recently and many features of their functionality and biology remain unknown. One of the important aspects is how their complex flower-like RBP structure is organized, functions, and evolves, and how the bacterial host evades jumbo phage infection.

In this project, we will investigate the aforementioned topics on two *Klebsiella*-specific jumbo phages (KAN and ϕKp24) as models. Applying advanced molecular microbiology, synthetic biology, and structural methods we will investigate these complex aspects at the protein level, the phage level, and the bacterium-phage interaction level. The experiments will be jointly implemented by the University of Wroclaw (**UWr - prof. Zuzanna Drulis-Kawa**) and Ghent University (**UGent - prof. Yves Briers**) with their partner at the Delft University of Technology (**TU Delft - prof. Stan Brouns**) who brings in unique expertise of bacterial immunity.

We are going to answer four specific research questions:
(1) What is the general organization of hyperbranched RBP systems in jumbo phages and how do they function?
(2) Are the hyperbranched RBP systems in jumbo phages static or dynamic?
(3) How do hyperbranched RBP systems evolve in jumbo phages?
(4) How do bacteria defend against infection by a jumbo phage equipped with a hyperbranched RBP system?

The research problems to be solved embody an ascending complexity, continuously accumulating proceeding insights toward a full understanding of the most advanced RBP systems. We want to accomplish to project in three work packages:
(1) Functioning and general organization of hyperbranched RBP systems at the protein level
(2) Dynamics of hyperbranched RBP systems at the phage level
(3) Jumbo phage - bacterial host interactions

With our existing expertise in the Klebsiella phage RBP subject, we will be introducing state-of-the-art research methods to advance the basic understanding of jumbo phage biology. Unravelling the organisation, dynamics, and evolution of the flower-like RBP systems of jumbo phages will be the basis for the identification or development of modern phage preparations effective in combating infections caused by MDR *K. pneumoniae* strains. Although the project focuses on typical basic research, its results will have a very significant economic and social impact, especially in the public health sector.