Since World War II, antibiotics have been routinely used to treat bacterial and fungal infections, and have contributed to saving millions of lives. However, many common infections are becoming harder to treat because microbes have naturally evolved to defend themselves against antibiotics. Antibiotics have also often been overused in treating humans, as well as in animal farming and agriculture. Such inappropriate usage has sped up the development of antibiotic-resistant strains, leading to a global rise in infections caused by multidrug-resistant pathogens, called superbugs. If no action is taken, it is estimated that by 2050, ten million deaths per year will be caused by superbugs.

Already in 2017, the World Health Organization published a list of key antibiotic-resistant pathogens, assigning them the highest priority status for the development of new drugs. However, the development of new antibiotic classes has not kept pace with the demand. Nowadays, drug-resistant pathogens are considered to be one of the biggest global threats to health and food security, affecting people worldwide. The economic burden is also substantial, due to increased healthcare costs and productivity losses.

The goal of our project is **to develop a new class of peptide-based antibiotics that will effectively combat drug-resistant bacteria**, thereby addressing one of the most pressing health challenges of our time and ensuring that we stay one step ahead of the superbugs.

We focus on developing improved versions of cell-penetrating peptides that normally penetrate cells without killing them. Using computer-aided design and machine learning, we will select short peptides capable of crossing membranes and will chemically modify them using multiple techniques: 'stapling' them into specific structures, creating disulfide bonds, and incorporating special amino acids. This will transform harmless cell-penetrating peptides into potent antibacterial compounds that should also eliminate biofilms.

We anticipate creating a library of new peptide-based antibiotics that are effective against drug-resistant bacteria and biofilms, biostable and safe for human cells, as well as less likely to induce bacterial resistance. We will determine how these chemically modified peptides pass through bacterial membranes and explore synergistic activities with existing antibiotics. We will identify the best peptide modifications, which enhance stability and antibacterial activity, while simultaneously eliminate toxicity to human cells. The tests will include checking whether the peptides can selectively eliminate only harmful bacteria while preserving beneficial bacteria. We will collaborate with leading computational scientists in Japan, using simulations to understand how these modified peptides work at the molecular level. The results of this project will also provide insights for future peptide-based antibiotic development.