iGEM Team Paris Bettencourt 2018

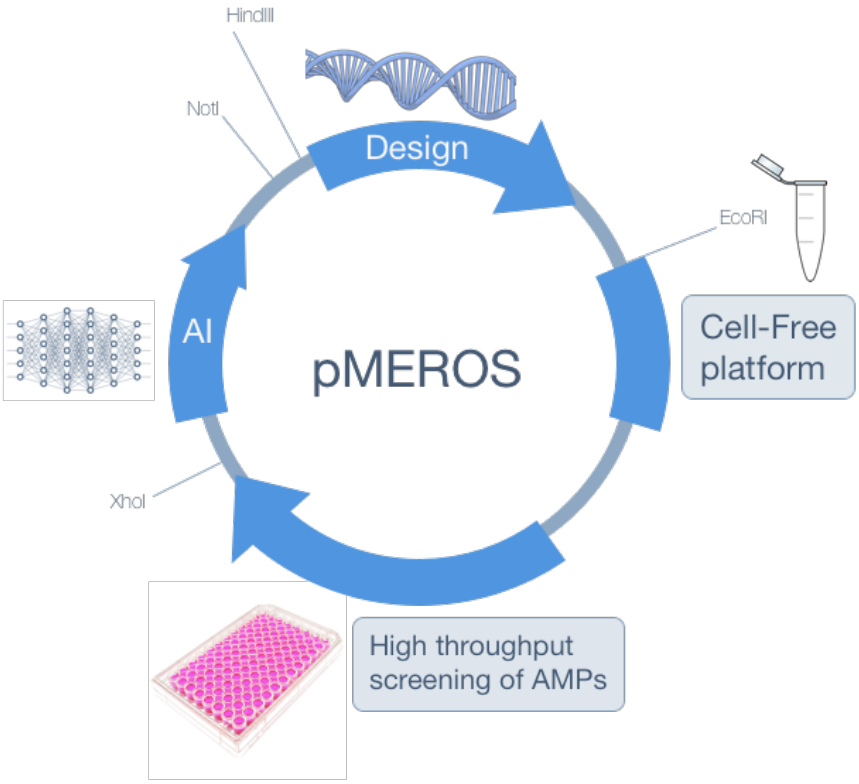
Fighting Antimicrobial Resistance with pMEROS

The emergence and spread of antibiotic resistance is a major public health concern and there is an urgent need for new antimicrobials against infectious diseases. However, developing a new antibiotic costs millions of dollars, and only a fraction of candidates is able to reach the market after over 10 years of research. A promising therapeutic alternative to antibiotics are antimicrobial peptides (AMPs). AMPs are a group of small peptides that are widespread in nature and found among all classes of organisms from bacteria to humans. Similar to antibiotics, AMPs have broad-spectrum activity, but resistance to them evolves slowly because they mainly target bacterial membranes. However, the current generation of AMPs has some important limitations, including potential toxicity to mammalian cells, and susceptibility to protease degradation. Also, the production of such short peptides relies on costly chemical synthesis that has a limited yield.

In this project, we aim to tackle these difficulties and improve naturally-occuring AMPs by engineering them into a star-shape polymer, which we have coined as pMEROS (*poly-* for "many" and *-meros*, "part" in Greek). Because pMEROS are made of proteins, we will be able to prototype their production inside a biological host. Consequently, by combining synthetic biology approaches and machine learning, we will reshape the methodology of new antimicrobial discovery, and greatly speed up its research and development, at lower costs. Specifically, we propose to accomplish the following objectives:

Aim 1: Bioengineering of efficient and safe-to-use pMEROS

pMEROS consist of multiple AMPs displayed on the surface of an oligomeric protein core that assemble spontaneously. The modularity of protein design allows cores and/or AMPs to be easily changed. This particular star-shape architecture could reduce the toxicity to mammalian cells while maintaining high antimicrobial efficacy. In addition, as a protein, the production of pMEROS does not depend on chemical synthesis and can be easily prototyped inside a tractable, inexpensive model organism. As a proof of concept, we will test pMEROS against a variety of infection-causing bacteria and bacterial biofilms, and also evaluate their safety to mammalian cells.



Aim 2: Building a user-friendly and rapid discovery pipeline for pMEROS

The existing discovery programs for small-molecule drugs is both time-consuming and expensive, because of the difficulty of chemical design and synthesis. pMEROS variants are relatively easier to design by simply switching the cores and/or AMPs. In this project, we will express and assemble these variants in the cell-free TX-TL system which is easy-to-use, cheap, and high-yield, in contrast to laborious and time-consuming traditional heterologous protein expression systems. The antimicrobial efficacy of the resulting product can be directly measured in our standardized, quantitative bactericidal assay. With this new pipeline, we can test millions of potential drug candidates in a much shorter time, as compared to classical antibiotic discovery workflows.

Aim 3: Developing artificial intelligence for computer-aided pMEROS design

The massive data acquired from the previously described pipeline will help to train a machine learning based artificial intelligence (AI) system. The trained system is able to generate new pMEROS that do not occur in nature. They may contain new peptide-core combinations and/or improved versions of AMPs that putatively will be used as novel potent and safe antimicrobials. The new designs will then be synthesized and tested using our experimental pipeline. By this recursion, we aim to develop numerous effective synthetic antimicrobials.

Public health relevance and social impact

The incidence of antibiotic-resistant infections has increased significantly in recent years and has become an important cause of morbidity and mortality in hospitals worldwide. The wide variability of naturally occurring AMPs, their amenability to both chemical and biological synthesis, as well as their easy optimization, besides their advantages in terms of antimicrobial activity compared to antibiotics, makes AMPs economically appealing antimicrobial compounds. This proposal takes an innovative biological strategy to develop novel antimicrobial compounds that effectively control bacterial pathogens and are more potent, less toxic, and easier to produce than existing antimicrobial peptides. We envision establishing pMEROS as a promising weapon to fight antimicrobial resistance.