# Ph.D. projects in progress

**1.**

**Mentor:** Csaba Pál, Bálint Kintses

**Doctoral school:** University of Szeged, Faculty of Science and Informatics, Doctoral School of Biology

**Ph.D. student:** Gábor Apjok

**Title of the research topic:** Developing new strategies for antibiotic-resistant pathogens using synthetic biology tools

**Description of the research topic:** The rapid spread of antibiotic resistant pathogenic bacteria represents an ever growing threat that will lead to serious healthcare disaster without taking action. It is expected to become the leading cause of death in the near future. The main reason behind this phenomenon is the i) irresponsible use of antibotics ii) slow discovery of novel antimicrobial agents iii) quick adaptation of pathogenic bacteria against antibiotics iv) and withdrawal of big pharmas from the researches for new drugs, among others. On the other hand, there are many tempting alternatives under excessive development. One such direction is the application of bacteriophages (phages). Phages are viruses that can specifically target and eliminate bacteria, and as such are prime candidates as therapeutic agents. Aside from killing bacteria, the potential of phages can be significantly expanded using synthetic biological tools. During the implementation of this project, the PhD student will apply synthetic biological techniques to increase the applicability of phages. The project aims the generation of mutant phages to infect the members of the so called 'ESKAPE' pathogens which are highlighted as the greatest challenge in current clinical practice.

**2.**

**Mentor:** Csaba Pál, Bálint Kintses

**Doctoral school:** University of Szeged, Faculty of Science and Informatics, Doctoral School of Biology

**Ph.D. student:** Mónika Számel

**Title of the research topic:** Assessing Resistance Evolution by Horizontal Gene Transfer against Antibiotic Therapies in Clinical Development

**Description of the research topic:** Resistance genes are typically discovered long after they have mobilized from the environmental resistome and spread widely in pathogenic bacteria. Despite the important medical relevance, however, there is no powerful method to prospectively test the resistome for specific genes that have the largest potential to spread horizontally among clinical pathogens against a novel antibiotic. Thus, to evaluate the acquisition

potential of mobile resistance genes into clinical pathogens we provide here a method that enables the large scale screening of the bacterial resistomes in clinical pathogens. With this technique, we provide evidence that it is possible to identify resistance gene families that are currently responsible for the majority of clinical problems without prior knowledge of the sequence of interest. Then, we test a diverse set of antibiotics that are in clinical development or have just been approved, and show that pre-existing resistance is already widespread in the mobilized resistome against these drugs.

**3.**

**Mentor:** Csaba Pál

**Doctoral school:** University of Szeged, Faculty of Science and Informatics, Doctoral School of Biology

**Ph.D. student:** Lejla Daruka

**Title of the research topic:** The investigation of the evolution of antimicrobial peptide resistance and the evolutionary interactions of antimicrobial peptides and antibiotics

**Description of the research topic:** The discovery of new antibiotics has slowed down significantly over the past 50 years, while the spread of multidrug-resistant bacteria is an increasing public health hazard. Antimicrobial peptides could be promising novel drug candidates against multidrug-resistant infections, however, in the absence of systems-level investigations, the development of peptide-based drug candidates is slow and often inefficient. The systematic investigation of the evolution of antimicrobial peptide resistance enables us to identify peptides, which could serve as a starting point for the development of resistance-free drug candidates. Moreover, by the examination of the evolutionary interactions ideal peptid-antibiotic combinations could be found that are effective against multidrug-resistant pathogenic bacteria. The project will require a high-throughput evolutionary experiment to study how and to what extent bacteria can develop resistance towards a divers set of antimicrobial peptides. Moreover, the project will include the systematic investigation of the evolutionary interactions of antimicrobial peptide resistant bacteria towards other peptides as well as conventional antibiotics. During the implementation of this project, the PhD student will learn the latest approaches from molecular and systems biology and utilize state-of-the-art synthetic biology methods and computational analysis.

**4.**

**Mentor:** Csaba Pál

**Doctoral school:** University of Szeged, Faculty of Science and Informatics, Doctoral School of Biology

**Ph.D. student:** Anett Dunai

**Title of the research topic:** Changes in antibiotic resistance in an antibiotic-free environment

**Description of the research topic:** The intensive and inappropriate usage of antibiotics has led to the increased frequency of multidrug resistance in both hospital- and community acquired infections. However, in the absence of antibiotics, resistance mechanisms generally confer deleterious effects, typically observed as an increased generation time and reduced survival inside the host. Nevertheless, bacteria can adapt to this new environment (that is the absence of the antibiotic) and increase their fitness. There are two possible ways bacteria can increase their fitness. It is either by losing/reverting the resistance or by maintaining their resistance through specific secondary mutations. The question is which way is more frequent and what is the molecular mechanism behind? During the implementation of this project, the PhD student will learn the latest approaches from molecular and systems biology and utilize state-of-the-art synthetic biology methods and computational analysis.

**5.**

**Mentor:** Csaba Pál

**Doctoral school:** University of Szeged, Faculty of Medicine, Doctoral School of Multidisciplinary Medical Scienses

**Ph.D. student:** Petra Szili

**Title of the research topic:** Changes in antibiotic resistance in an antibiotic-free environment

**Description of the research topic:** The intensive and inappropriate usage of antibiotics has led to the increased frequency of multidrug resistance in both hospital- and community acquired infections. However, in the absence of antibiotics, resistance mechanisms generally confer deleterious effects, typically observed as an increased generation time and reduced survival inside the host. Nevertheless, bacteria can adapt to this new environment (that is the absence of the antibiotic) and increase their fitness. There are two possible ways bacteria can increase their fitness. It is either by losing/reverting the resistance or by maintaining their resistance through specific secondary mutations. The question is which way is more frequent and what is the molecular mechanism behind? During the implementation of this project, the PhD student will learn the latest approaches from molecular and systems biology and utilize state-of-the-art synthetic biology methods and computational analysis.