Identification of the key genetic determinants of *Staphylococcus aureus* bacteraemia and related complications

Staphylococcus aureus is a pathogenic bacterium and a leading cause of bloodstream infections worldwide. *S. aureus* bacteraemia (SAB) is difficult to treat, often associated with complications, incl. infective endocarditis, osteomyelitis and recurring infections and results in high mortality. *S. aureus* is primarily a commensal and an asymptomatic colonizer of ca. 30% of human adult population which increases the risk for infection, such as on implanted medical devices. Recommendations for the clinical management of SAB are often limited to an immediate removal of infection foci and a prolonged antibiotic therapy, the choice of which is limited by the global crisis in spreading antibiotic-resistance.

This project will identify the key genetic elements associated with the development of bloodstream infections caused by the bacterium. Understanding of the complexity of staphylococcal pathogenicity mechanisms requires a truly comprehensive approach. We will use a novel and comprehensive approach, called genome wide association (GWAS), that links bacterial genomic data with patient's clinical manifestations as well as results obtained in laboratory investigation of the bacterial adaptation traits. GWAS uses a multi-stage bioinformatic and statistical analyses in order to identify the unique genetic elements associated with the disease. In our analysis, we will use hundreds of bacterial isolates obtained directly from patients with bloodstream infections. We will use isolates belonging to genetic groups that dominate among infections in Poland I order for better understanding of specificity of the local infections. To understand and score each isolate's pathogenic potential information on isolate's associated clinical manifestations in patients (incl. information on the source of infection, whether the patient is a carrier or if there are additional diseases) will be analysed. In order to identify more precisely the elements associated with evolutionary adaptation of the virulent bacterial isolates we will characterize their traits in the lab (incl. fitness blood, binding to human plasma proteins or biofilm formation) using experimental methods and conditions that mimic the infection. We will use methods for simultaneous characterization of many bacterial isolates. We will then map genomic elements with the relevant clinical and phenotypic traits of each isolate performing the GWAS analysis, which will be carried out using bioinformatic tools and computational modelling, to identify the key genetic factors that are associated with the disease development. Our findings will be validated using molecular biology methods, such as using bacterial mutants that are defective in the production of those virulence factors. We will make them in the lab by silencing the relevant bacterial genes to confirm the role of a specific factor in a disease-relevant phenotype.

The project will also examine the possibility of detecting the infection-mediated changes in small molecules composition of infected patient's blood (metabolomic profiles) to diagnose the infection and type of bacterium. This would allow a breakthrough rapid diagnostic strategy and would be an invaluable improvement of the treatment process.

The study will be carried out at the University of Warsaw in collaboration with experts in bioinformatics and microbiology of staphylococci, respectively from the London School of Tropical Science and Trinity College Dublin. The research on the use of metabolomic markers, on the other hand, will be carried out in cooperation with the Medical University of Wroclaw. Recognizing the key factors that promote *Staphylococcus aureus growth* in the blood will be a milestone in the way of generating preventive therapy that inhibits the development of blood infections. It could serve as an alternative or support for traditional antibiotic therapy and reduce the incidence of blood infections.