The research on the use of novel analogues of endogenous antimicrobial peptides in therapy of staphylococcal skin infections

Skin infections caused by staphylococci are the most difficult to treat in the clinical aspect. *Staphylococcus aureus* has a unique ability to cause a broad spectrum of illnesses and symptoms like skin and soft tissue infections, toxic shock syndrome, bacteremia, endocarditis and inflammation of the lungs or bones. It has been estimated that in the United States staphylococci every year infect about half a million people, and in 2003 the cost of their treatment estimated 14 billions of dollars. The bacteria of this species produce a number of mechanisms allowing them to invade into the organisms, including the avoidance of opsonization by antibodies and complement system, disruption of chemotaxis and lysis of neutrophils. Because of their ability to survive inside leukocytes, infections tend to move into a chronic stage and recur after recovering. The therapy often takes many years and commonly tends to be ineffective. An additional complication of the therapy is the formation of the biofilm - the organized three-dimensional structure that is characterized by enhanced resistance to antibiotics. It is estimated, that approximately 65% of hospital infections is associated with the formation of this type of structures.

Inappropriate use and misuse of antibiotics induces the appearance of strains resistant to traditional antibiotics. The most dangerous of these are: methicillin-resistant *Staphylococcus aureus* (MRSA), coagulase-negative staphylococci (CNS), penicillin-insensitive pneumococci and vancomycin resistant enterococci (VRE). Bacteria of the genus *Staphylococcus aureus* constitute a serious clinical problem due to their particular ability to acquire resistance to antibiotics. The vast majority of *S. aureus* isolates is resistant to penicillin and ampicillin but in the recent years strains resistant to clindamycin or even erythromycin were also reported. Moreover, some studies indicate the occurrence of resistance mechanisms to mupirocin or fusidic acid. To date, these two antibiotics were considered as the most effective in topical treatment of skin diseases caused by staphylococci. A big surprise was also the appearance of vancomycin-resistant *S. aureus* (VRSA) in chronic venous ulcers. Among these strains the resistance to linezolid and streptogramins was also reported. According to the incidences of VRSA, vancomycin is no longer perceived as a reliable drug against all clinically important Gram-positive bacteria. Over the few past years, new antibiotics were developed such as glycopeptides: telavancin, dalbavancin, otrivancin or β-lactams: ceftaroline and ceftobiprol which are effective against MRSA. However, these are systemic drugs with a plenty of side effects. Moreover the use of them in therapy is quite expensive. Taking into account the fact, that most of the skin bacterial infections require local therapy, the search for new compounds for such application is on a rise. Equally significant is also the ability to eradicate bacterial biofilms. Antimicrobial peptides are compounds that exhibit such properties.

The purpose of the Investigators' project was to design, synthesize and thoroughly examine analogues of endogenous antimicrobial peptides such as LL37, human lactoferricin and their conjugates with lipopeptides for use in the treatment of skin diseases caused by staphylococci.

All synthesized peptides will be subject to microbiological assays including tests on reference and clinical strains. Clinical strains will be obtained from patients with diagnosed skin infections. LL37 will be used for comparative studies where necessary. In the case of the most effective compounds as far as the impact on the formation of biofilms is concerned, their resistance and toxicity will be investigated. In the next stage conformational studies of the peptides will be carried out to determine their structure and to find features responsible for their specific properties. After determining the structure - activity relationship for investigated peptides the penetration study through the skin will be performed for selected analogues. It will be determined *in vitro* if there is any potential to use this type of compounds in the future in the treatment of local skin diseases caused by staphylococci.