Summary

Antimicrobial peptides (AMPs) are key components of the innate immune system. AMPs are short, cationic peptide chains found in bacteria, plants, amphibians, insects, fish, and mammals. They exert their activity primarily by targeting microbial cell membranes, leading to membrane destabilization and, consequently, cell death. Due to their broad-spectrum activity, AMPs are being investigated as potential therapeutics for bacterial infections, particularly in addressing the growing problem of antibiotic resistance.

The human cathelicidin LL-37 is the only known antimicrobial peptide naturally present in humans. It exists initially as an inactive precursor, hCAP18, which is proteolytically cleaved by proteinase 3 to generate the active form. LL-37 is a linear, cationic peptide with an α-helical secondary structure. Its name refers to its primary structure, which starts with two leucine residues at the N-terminus and comprises a total of 37 amino acids. Cathelicidin exhibits multiple biological functions, including involvement in the formation of neutrophil extracellular traps (NETs), angiogenesis, apoptosis, as well as antimicrobial, anticancer, and immunomodulatory activities.

As part of this doctoral dissertation, the native structure of LL-37 was modified by selectively substituting residues of arginine, lysine, isoleucine, and phenylalanine with DAPEG building blocks i.e., *L*-2,3-diaminopropionic acid (DAP) derivatives functionalized in their side chains with appropriate oxoacid residues. These modifications altered the hydrophobicity of the peptide chain, which in turn influenced its antimicrobial activity. The presence of longer side chains at the modified positions, compared to native LL-37, conferred increased resistance of the peptidomimetics to degradation by peptidylarginine deiminases.

The synthesized analogues were analyzed using circular dichroism spectroscopy to verify that the introduced modifications did not disrupt the α-helical secondary structure of the peptide. Additionally, electrophoretic mobility shift assays (EMSAs) confirmed that the modified peptides retained their ability to bind plasmid pUC19 DNA and double-stranded DNA (76 bp) comparably to the native LL-37.

Furthermore, the peptidomimetics were evaluated for their enzymatic activity in order to determine their functional roles in relation to HL-60 cells differentiated toward a neutrophil-like phenotype. The resulting compounds [Dap(MO1)^{13,20,24}]LL-37,

[Dap(MO2)^{13,20,24}]LL-37, and [Dap(O2)^{8,10,12,15,18,25}]LL-37 demonstrated activating effects on the differentiated cells.