First steps to ESKAPE microbial resistance

Antimicrobial peptides: structure-activity relationships and antimicrobial mechanisms

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In Short

- New antibiotics are needed to overcome the global health challenge of microbial resistance.
- Antimicrobial peptides are promising candidates against multidrug-resistant bacteria.
- The antimicrobial mechanisms based on their structure-activity relationship are often unknown.
- Advanced sampling MD simulations are going to elucidate the mechanisms of interaction of one antimicrobial peptide with the bacterial membrane.

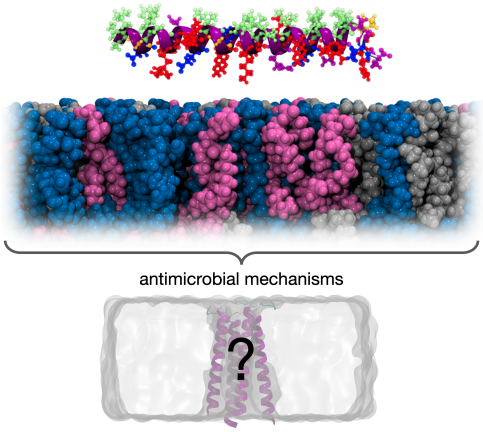

Figure 1: *Visualization of antimicrobial peptide SAAP-148 on a bacterial inner membrane. Their interaction is at the basis of the antimicrobial activity and it is the subject of this project.*

Infections are a major concern in global healthcare, especially from bacteria that form biofilms. Their presence can for instance lead to the establishment of chronic wounds, which cause persistent inflammation and damage and can ultimately result in death.1 In particular, multidrug-resistant bacteria, that are difficult or even impossible to treat, have evolved increasingly into a global health threat,[1] with special emphasis on strains that belong to the so-called ESKAPE panel.[2] Around 2.4 million people in Europe, North America and Australia are expected to die due to infections with resistant microorganisms in the next 30 years. Moreover, clinically relevant bacterial biofilms are commonly polymicrobial, which makes them harder to treat, and demonstrate adaptive bacterial resistance. Their treatment has an immense impact on healthcare systems worldwide and consequently on the global economy, with estimated costs of 3.5 billion US$ per year. According to the WHO priority list, future development strategies should therefore focus on antibiotics and their alternatives that are active against "critical-priority" bacteria, especially multidrug-resistant and Gram-negative bacteria.

It was recently shown that antibiotic resistant bacteria have a high propensity towards a collateral sensitivity against so-called Antimicrobial Peptides (AMPs).9 AMPs are short-chain, cationic peptides with a large proportion of hydrophobic residues (>30%).[3] AMPs evolved as a host-defense mechanism and are conserved in all kingdoms of life.[4] Essential to their usage to combat bacterial resistance is the fact that bacteria have been exposed to AMPs for millennia and, with few exceptions, general resistance mechanisms are yet to arise. Taken together these properties make AMPs excellent candidates for the functionalization of biomaterials and medical devices.

Understanding the mechanisms behind AMP antimicrobial action is crucial for their application, since their bactericidal activity might otherwise be lowered or lost. A complex interplay of physicochemical and structural parameters mediates the antimicrobial performance of such peptides, including size, composition, overall charge, hydrophobicity, amphiphilic character and conformation. It was previously shown that antimicrobial activity is strongly correlated to peptide conformation (structure activity relationship) or, more precisely, to their induced amphipathic conformation upon membrane interaction.[5]

For this reason novel design principles based on the concept of "form follows function" have been considered. We propose the often-neglected issue of peptide conformation is crucial to preserve during both material functionalization and application in the body in order to ensure that the highest antimicrobial efficacy is maintained.

A promising candidate for computer-assisted AMP design, is the synthetic oligopeptide SAAP-148. Within this project we want to understand the atomistic details of the conformational ensemble of SAAP-148 in solution and upon interaction with the membrane. Based on these results we want to identify potential interaction mechanisms. We will focus on the application of enhanced sampling methods to overcome the timescale problems described in previous approaches. In accordance with the WHO

priority list8 we will focus on a critical priority bacteria: *Pseudomonas aeruginosa*. This species represents significant challenge for treatment as it is prone to form biofilms and is commonly associated with antimicrobial resistance (belongs to the ESKAPE panel).[2]

The general question we aim at answering during the proposed project is: How do the conformational ensemble and the membrane-induced conformational changes influence the antimicrobial action of an antimicrobial peptide? We plan to tackle this question by:

1) investigating the conformational ensemble of SAAP-148 in solution with a focus on realistic solvent conditions,

2) building inner and outer bacterial model membranes,

3) identifying the induced amphipathic conformation upon membrane interaction of SAAP-148, and

4) approaching the mechanisms of antimicrobial actions of SAAP-148.

We will use Molecular Dynamics simulations, coupled with state of the art enhanced sampling methods to investigate the complex conformational landscape of this system.[6,7]

We believe that the obtained results, although obtained for a selected peptide and an exemplary outer and inner membrane composition of a gram-negative bacteria, will be of general interest within the larger microbiological and (bio)material community, adding caveats to the extrapolation of results from experimental assays and providing a better atomistic understanding of the antimicrobial mechanisms of AMPs.

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More Information

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Project Partners

The Hancock Lab, Centre for Microbial Diseases and Immunity Research, Lower Mall Research Station, Vancouver, B.C. (Canada); Biomolecular and Materials Interface Research Group, Interdisciplinary Biomedical Research Centre, School of Science and Technology, Nottingham Trent University (UK)