Antibiotics: Molecular dynamics simulations of the structure and function of Lantibiotics and other antimicrobial peptides (AMPs)

Antibiotics: Molecular dynamics simulations of the structure and function of Lantibiotics

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In Short

- Experimental studies have reported the efficiency of the AMPs against multidrug-resistant bacteria, but there is a lack of knowledge regarding their mechanism of action. Therefore, the atomistic details achieved through the analysis of the trajectories will contribute to the rational design of new antibiotics with increased bactericidal activity.
- Study of the molecular mechanism responsible for the antibacterial activity of class I- and class II-lantibiotics at an atomic level, as well as the dynamic properties and aggregation states of antimicrobial peptides (AMP) generated by humans.
- Conventional molecular dynamics (cMD) simulations of "non-modified-" Lichenicidin lantibiotic interacting with the substructural unit of the peptidoglycan layer, Lipid II molecule, and with the phospholipid membrane of a bacterial cell.

Only in Europe, approximately, 25,000 people die from a *superbug* per year. The current antibiotics have lost effectiveness against these multidrug-resistant bacteria which is why the necessity of developing new antibiotics is an urgent worldwide issue. As alternative to the existing antibiotics, the attention has been focused on the antimicrobial peptides due to their efficiency showed against the multidrug-resistant bacteria. Unfortunately, despite that several mechanisms of action have been proposed such as: carpet model, barrel-stave, toroid-pore mechanisms among others [1], there are still unanswered questions on how its bactericidal activity takes place. Shedding light at atomistic level about their *modus operandi*, the design of more potents drugs will be available providing, therefore, new weapons to fight the global crisis generated as a consequence of the antibiotic resistance.

A large variety of organisms generate AMPs such as plants (e.g. thionins), amphibians (e.g. magainins), insects (e.g. cecropins), fungi. Our research is focused on the study of the antimicrobial activity of AMP generated by bacterias, commonly named bacteriocins [2], and in those expressed by humans, concisely, focused on the cathelicidin and defensins families [3].

Among all types of bacteriocins discovered so far, our work is centered in the **Lantibiotic** family. Lantibiotics are antimicrobial peptides (AMP) which are ribosomally synthesized and posttranslationally modified peptides (RiPPs) to their biologically active forms. During the posttranslational modifications the thioether amino acids lanthionine and methyllanthionine are introduced. Therefore, the term *lantibiotic* is derived from lanthionine-containing antibiotics.

The bactericidal activity of most lantibiotics lies on targeting components of the plasma membrane of bacteria, in particular **Lipid II**, which is responsible for the cell wall synthesis. While type I permeabilizes the bacterial plasma membrane via interaction with Lipid II, the class II lantibiotics may also trigger bacterial death via interaction with Lipid II by means of a still unknown mechanism.

Specially challenging is the study of the antibacterial activity of so called two-component lantibiotics, such as **Lichenicidin** consisting of an α and β **components**. In this context, it has been hypothesized that both α and β components act synergistically interacting with the Lipid II molecule, blocking the cell wall synthesis, among other factors, leading to the bacterial death. However, the molecular mechanism is still unclear.

Conventional all-atom Molecular Dynamics (cMD) simulations have been carried out to study the structural characteristics and modes of action of two types of lantibiotics: i) Nisin (figure 1) [4] and ii) Lichenicidin (figure 2) [5].

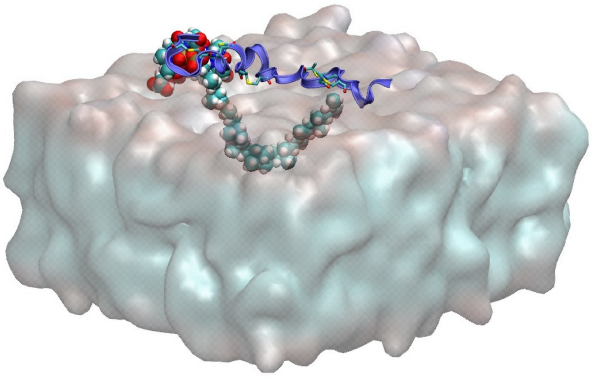

Figure 1: *Nisin lantibiotic Lichenicidin attached to Lipid II*

Nisin lantibiotic was selected to validate the theoretical approach because it is a well theoretically and experimentally investigated lantibiotic while Licheni-

cidin was chosen representing the two-component lantibiotic family.

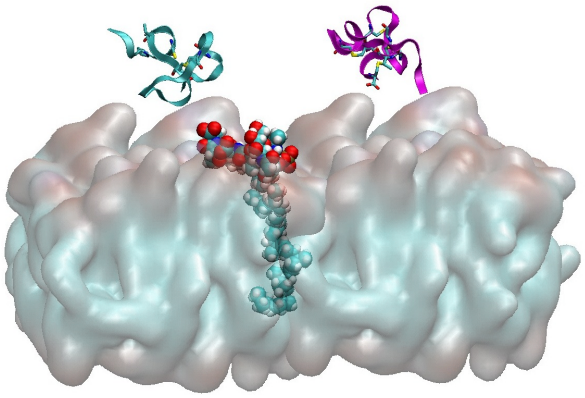

Figure 2: *Two-component lantibiotic Lichenicidin-* ***Lch***α *and* ***Lch***β*- and Lipid II inserted in a POPG/ POPE membrane.*

Lichenicidin is produced by different strains of Bacillus Licheniformis and it is composed of the peptides **Lch**α and **Lch**β which act synergistically against Gram-positive bacteria. The theoretical model system was, therefore, developed using a lipid membrane composition mimicking a Gram-positive environment.

Furthermore, the current worldwide need of new antibiotics has promoted the opening of a new research line focused on **AMPs generated by humans**. Humans are able to synthesized three different classes of AMPs: the **defensins**, the histatins and the **cathelicidin**.

In the human defensin family, two classes are found: α-defensins and β-defensins. In our study has been considered the β-defensin family, concisely, the hβD3 peptide and two synthetic mutants, namely hβD3-c and hβD3-l. These two variants were designed in order to evaluate the impact of modifications in the ring pattern structure in the peptide dynamics and membrane attachment.

Contrary to the defensin family, the human catelicidin family is exclusively represented by a single peptide, called LL-37. Our study at atomistic level covered this unique peptide and two fragments derived from it (figure 3). Additionally, this section has been successfully compared with spectroscopical measurements carried out by our collaboration partners at the Technical University Berlin and Leibniz-Zentrum Borstel.

In parallel, the cathelicidin project has been extended to three derivatives inspired on LL-37. This investigation is being developed in collaboration with research groups in Austria and the Netherlands.

The computational study of the various types of AMPs carried out in this project will contribute to the rational **design and modelization of novel antibiotics with improved properties**. Moreover, as the

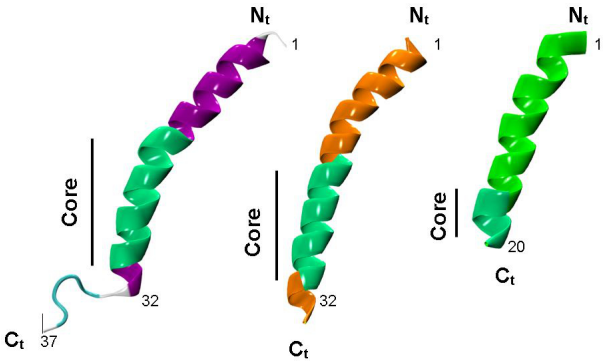

Figure 3: *Cathelicidin LL-37 and its fragments namely LL-32 and LL-20*

bactericidal activity of new antimicrobial agents is still unknown, molecular dynamics (MD) simulations can provide an initial molecular architecture of the engineered lantibiotic/AMPs.

WWW

http://www.modeling.tu-berlin.de/

More Information

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