Exploring the conformational space of cationic antimicrobic peptides

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The number of new antibiotics being released on the market in the last decades has dramatically decreased, whilst on the other hand we assist to a constant increase of multi- or even pan-drug resistant bacterial strains. There is the risk of returning to a pre-antibiotic era, with childbirth of even small surgical procedures becoming a life threat once again. [1] There is therefore an urgent need for new antibacterial drugs.

Cationic peptides with net positive charge at neutral pH have promising antimicrobial activity. However, very few entered into clinical trials due to their poor bioavailability and toxicity.[2]

The aim of our work is to investigate and compare the structures of such peptides, in order to identify the presence of common features, both in terms of recurring patterns in the amino acid sequence and 3D structure similarity. These data will then be used to design novel peptido-mimetic molecules with antibiotic activity.

A set of short sequence antimicrobial peptides with activity against Gram-negative bacteria was generated and cross-referenced against available databases. A multiple sequence alignment of such peptides was carried out and the repetition of the WKW, FRF and FKF patterns was observed with high frequency.

Initial 3D structures of peptides with sequences longer than 9 amino acids were predicted using PEP-FOLD online server, while the conformations of 7 and 8 amino acids long peptides were obtained using simulated annealing instead. Further molecular dynamics simulations of all peptides were carried out in presence of the solvent, salt and at relevant pH to mimic physiological conditions. Both the simulated annealing and the MD simulations were performed with Desmond, using Maestro (Schrödinger) as graphic user interface.

The MD trajectories are being analysed and representative conformations will be superimposed to investigate the presence of common features in terms of shape and electronic distribution. The identified recurring patterns in the amino acid sequences and their 3D molecular similarities will allow us to design peptido-mimetic molecules which will hopefully provide us with a lead to more effective and less toxic antibiotic drugs.

1. Liu, Y.-Y., et al., Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. *The Lancet Infectious Diseases*, **2016**, *16* (2): p. 161-168.
2. Hancock, R.E.W., Peptide antibiotics. *The Lancet*, **1997**, *349* (9049): p. 418-422.