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TITLE:
Design of Antimicrobial Peptides to Fight Antimicrobial Resistance

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ABSTRACT TEXT:
The value of an antimicrobial peptide (AMP) hinges on its ability to fight bacteria at low minimal inhibitory concentration (MIC) and to simultaneously exhibit a low toxicity to eukaryotic cells. In addition, demands like proteolytic stability and solubility in aqueous media under in vivo conditions must be considered. Such prerequisites can be met by short amphipathic peptides whose surface is packed with positively charged side chains on one hemisphere and apolar amino acid side chains on the other and which adopt helical conformation upon interaction with bacterial envelope structures. Such membrane active peptides interact with target microorganisms by cooperative binding to negatively charged lipids and subsequent disruption of the bacterial membrane. Resistance against this mode of action is not likely to occur, at least AMPs remain effective in the defence against pathogens despite they are most ancient antimicrobial agents. However, specificity of naturally occurring AMPs usually is not convenient for medical use and high activity against bacteria in many cases is accompanied by high toxicity. Hence, custom tailored highly effective AMPs with low toxicity are required for medical purposes.
With this in mind, we are developing AMPs that match the above design criteria. In order to identify suitable peptide candidates we devised an evolutionary molecular breeding approach. First, a selection of 49 linear 20mer candidate AMP sequences was synthesized in µmol amount on solid phase. Their MIC against 3 selected bacterial strains (P. mirabilis, K. pneumonia and E. coli WBB01) was quantified and haemolysis of red blood cells was investigated for all candidate peptides. All datasets were merged to global fitness values. Next, an evolutionary algorithm (EA) was employed to create recombined and mutated peptide sequences which were again synthesized and tested. Finely tuned parameter settings for the EA were elaborated which enabled a stepwise decrease of the MIC as well as the haemolysis rate of the peptides in 5 consecutive rounds of evolutionary optimization. This is reflected in an increase of overall fitness of optimized peptides as shown in Figure 1.

KEY WORDS:
Antimicrobial Peptide; evolutionary optimization; membrane disruption.

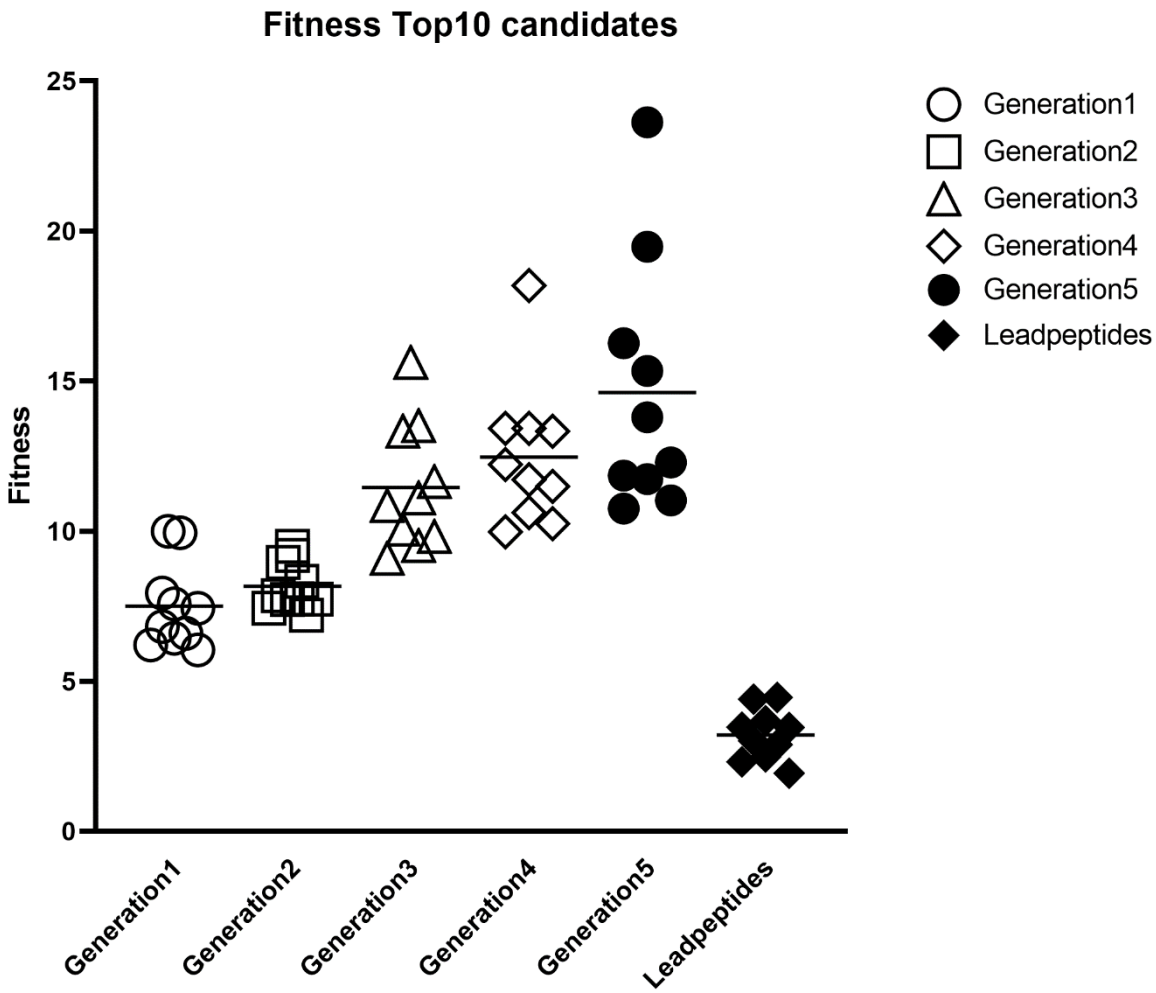
Fitness Top10 candidates
Fitness
25
20
15
10
5
0
Generation1
Generation2
Generation3
Generation4
Generation5
Leadpeptides
Generation1
Generation2
Generation3
Generation4
Generation5
Leadpeptides

Figure 1