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Perspective

Antimicrobial Peptides Surrogates

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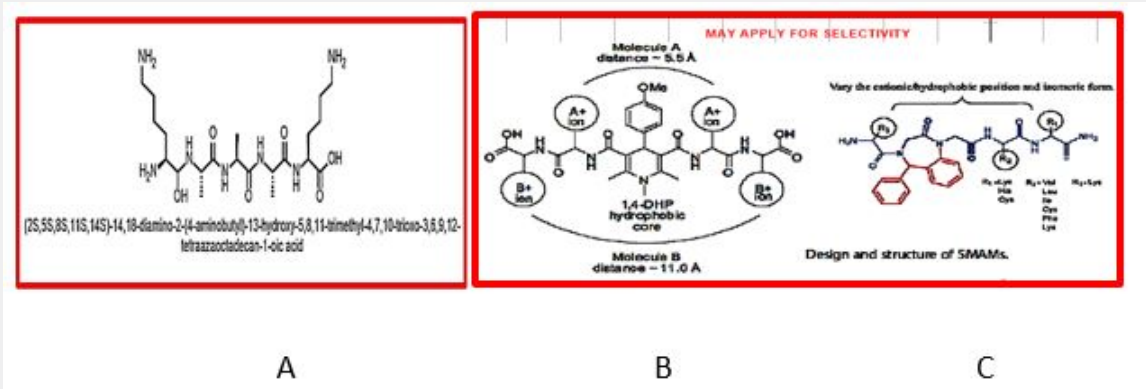
Introduction

The Fast Development of a microbial nosocomial pandemic that is in many cases estimated today to cause a dramatic increase in morbidity of people that contracted microbial infections caused mainly by bacteria are part of the innate immune response found among all classes of life. The Antimicrobial peptides (AMP) [1] are also called host defense peptides, of which 2000 different short (5-50 amino acid sequences) polypeptides were isolated and identified. The current situation with antibiotic drugs is quite alarming. Some bacteria have become resistant to all medicinally applied drugs. It includes the Gram-positive bacteria classified as Methicillin-resistant Staphylococcus aureus (MRSA) and the Gram-negative group in the Carbapenem-resistant Enterobacteriaceae group (CRE).

In 1948 Synge [2] reported on the Synthesis of Some Dipeptides Related to the AMP Gramicidin S. The dipeptides were required to study the structure of gramicidin S. in the frame of his efforts to learn about the very high antibacterial activity of the cyclic peptide.

Currently, AMPs represent one of the most promising future strategies to combat infections and antimicrobial drug resistance. This is evident by the increasing number of studies these peptides are subjected to. As our need for new antimicrobial drugs becomes more urgent, the question remains: can we develop new drugs based on the design principles of primitive molecules? [3]

The advantage of the AMP is that most of them act in the broad eradication spectrum of bacteria in a new mechanism that is less likely to allow the development of resistant strands of the microbes. However, today many means [4]. Many undesired features ore uncovered while examining occurring natural AMPs. Efforts-based drug compounds suffer from a drawback that could jeopardize efforts for therapeutically use: they are not straining selective [5], kill the "good" and the "bad" bacteria with a similar efficiency [6]. Eradication of all bacteria takes place with equal efficiency [7,8]. To overcome the drawbacks and introduce features not present in the AMPs themselves. One of the famous AMPs is the from the skin of an African todd isolated Magazine. The company that was established with the same name realized the antimicrobial therapeutic potential in mimics of the natural Magazine, namely a semisynthetic polypeptide Paxiganan [9] as the analog of Magazine. Surrogate agents that are Mimics of AMPs are collectively called peptidomimetics. The types of modifications introduced are generally modeled after the structural requirements known to influence AMP activity. Attempts to conserve features like positive charge and amphipathicity are made to ensure the antibacterial activity of the mimetic compounds. The mimics are often constructed with a different backbone (i.e., not based on a-amino acids) or may carry dislocated side chains to overcome the low bioavailability and lack of metabolic stability found for traditional AMPs [10].



The quest for preferential eradication focused our interest on finding: that an antibacterial motif, namely Lys-Ala-Ala-Ala-Lys A, identified in Dermaseptin S4 could be mimicked. Its surrogates show similar broadband [11] antimicrobial activity B and C [12], particularly compound C, where the β-turn mimics benzodiazepine incorporated into the hydrophobic part of the molecule.

Usually, the naturally operating innate immune system is composed of many amino acids at a particular sequence. Only a short sequence was found to possess most of the antimicrobial potential. A general presentation of a typical process toward a Surrogate for the naturally active polypeptide [13] is as follows:

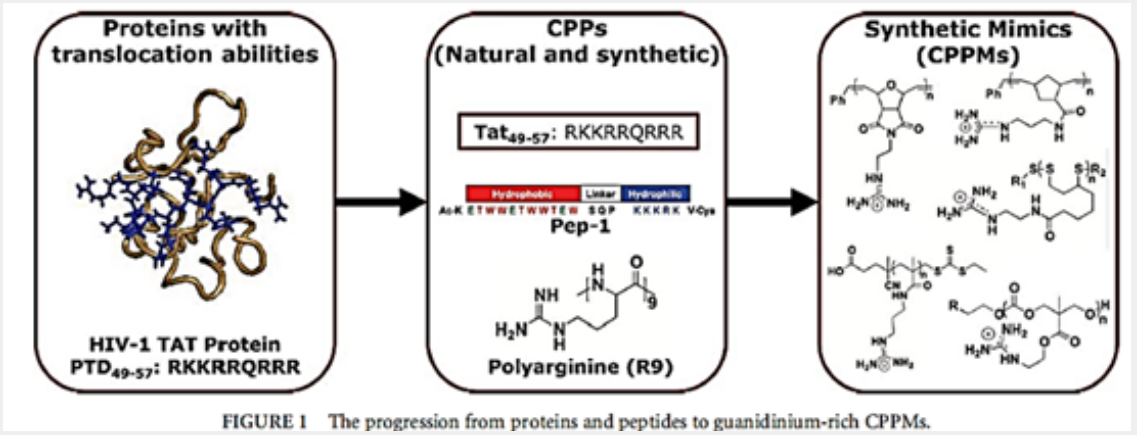
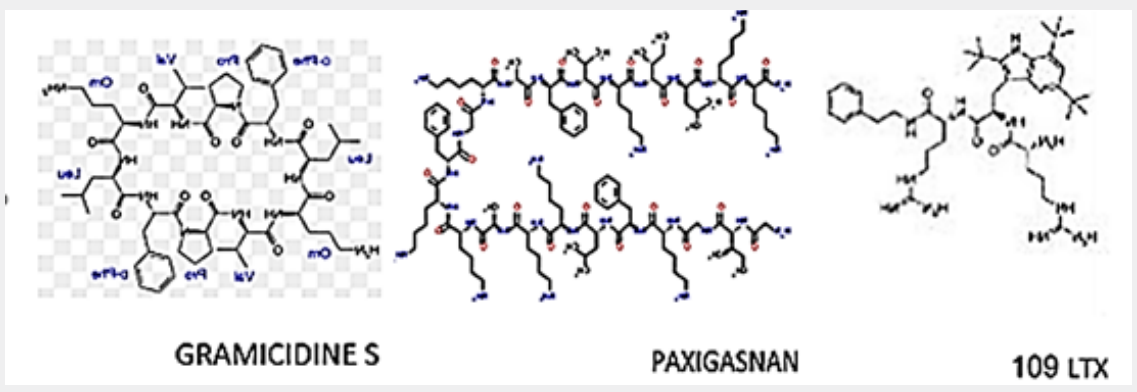


FIGURE 1 The progression from proteins and peptides to guanidinium-rich CPPMs.

Figure: *The progression from proteins and peptides to guanidinium- rich CPPMs*

Strains of the bacteria that harm are becoming more resistant to drugs but also live in the vicinity, in the same organism, as other useful and needed fauna of microorganism exist in human gut, the "beneficial" various strands of Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria for example. We would like to selectively eradicate the "bad" microorganisms and leave the "useful" ones intact [14]. Currently, one of the highest hurdle in the race to application is the needed selectivity in the eradication of germs. Mitsuzaki and others have investigated the possibility of cell selectivity [15]. The interactions of an AMP with the membrane can¬not be explained only by a particular sequential amino-acid pattern or motif; rather, they originate from a combina¬tion of physicochemical and structural features [16] including size, residue composition, overall charge, secondary structure, hydrophobicity and amphiphilic character [17].

Today, Mimicking the antimicrobial activity of AMPs has entered the stage of application as topical drugs, this due to the non selective eradication of microbes. In this respect, application of GramicidinS was followed by Paxiganan and the newly manufactured LTX 109, are practically a very broad spectrum microbe's eradication agent with limited medicinal value due to lack of selectivity. They kill them all.

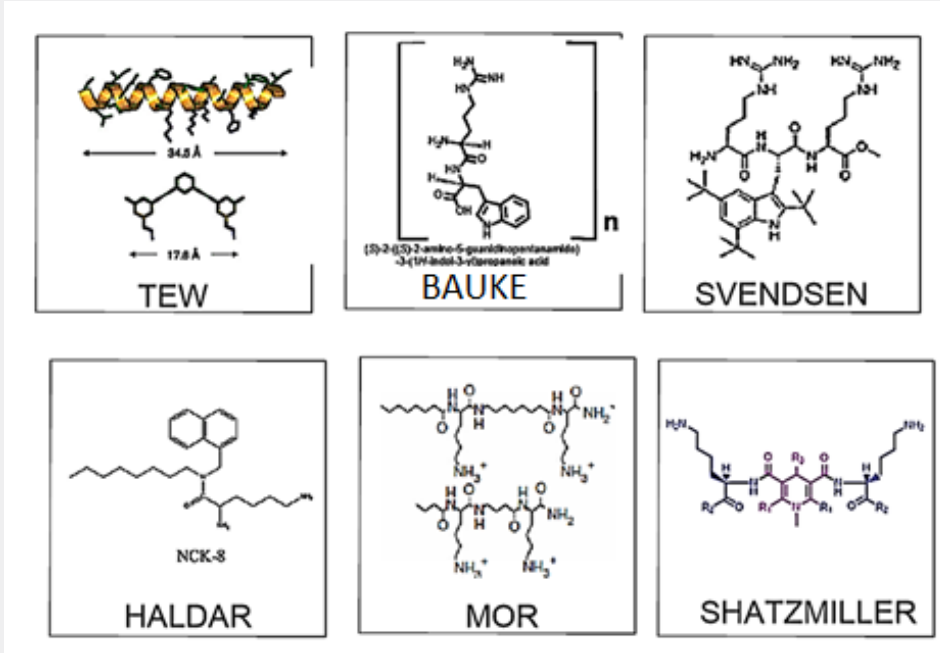


It is believed that cyclic form of AMPs contributes to their extraordinary high eradication ability [18] by a hydrogen-bonded tubular architecture of the self-assembled, eight-residue cyclic D,L-a-peptide, and modes of membrane permeation accessible to peptide nanotubes.

The current situation focuses on a few research efforts that handle small molecules with molecular weight around 400-500 and i8n respecting the rules of LipinskI rule of 5 [19].

Surrogates of shoet peptide sequences for drug like agents.

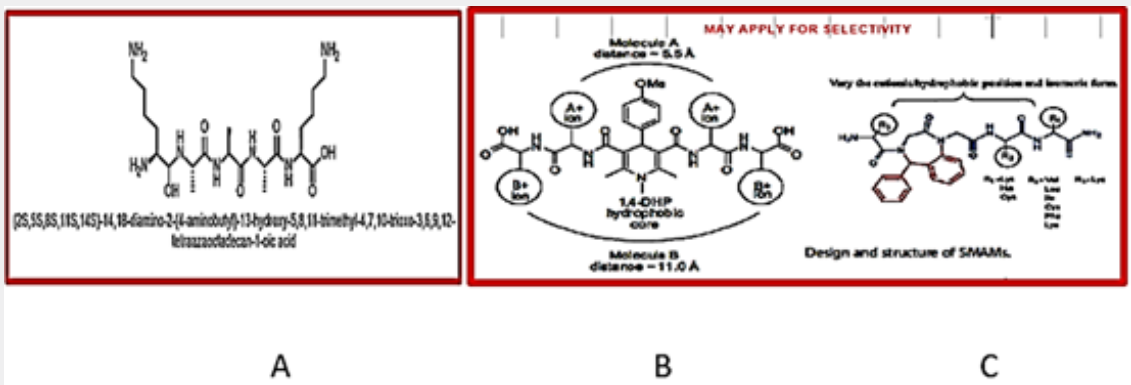
The effort in this frame was to identify short bioactive (antimicrobial) peptide sequences and in AMP from various sources (Human, Amphibians, Fish, insects, Serial etc. In the following drawing are represented a few structure of antimicrobial surrogate structure that were designed on the basis of natural motifs found in AMPs.



Tew [20] and his colleagues designed the tricyclic aromatic structure on the basis of the general idea of amphepatic nature of AMP in particular the work of Vogel [21]. Park [22] and Bauke [23] explored the motifs WK and WR respectively as unit for the eradication of bacteria. Svendsen ans partners established a corporation for the development of antibacterioal medicins based on Lactoferricin turn [24,25]. On this basis the Topical drug molecule LTX 109 was developed by Svendsen and the people from LYTX [26]. Haldar and his group incestigated the use of [27] Aryl-Alkyl-Lysines as Agents That Kill Planktonic Cells, Persister Cells, Biofilms of MRSA and Protect Mice from Skin-Infection. Mor and his coworkwrs applied a lysime amphipathic unit to construct antimicrobial polymers [28].

FIG. 1. Primary structure of LfcinH. Edman degradation was performed with fragments of the peptide obtained by trypsin digestion. Segments in bold were detected. The six N-terminal amino acids (GRRRRS) had previously been verified by N-terminal Edman degradation of the intact protein.

Shatzmiller and the group have identified a simple sequence of 5 amino acids in the structure of Dermaseptin S5, namely Lys-Ala-Ala-Ala-Lys. A, this was the basis for the design, synthesis and evaluation of the surrogates B and C whereas C contains a β-turn mimic as moiety [29].



There is a complex situation regarding the mechanism of action in which AMP eradicate the bacteria. The Mitsuzali-Shai-Huang membrane disruption mechanism [30] has become the domain of not all the AMPs. Many may disintegrate membranes but it is clear today [3].

The way Surrogates corrupt the cell membrane may become a high hurdle in the process of AMPs to become the future antibiotic drugs. In their considerations. Researchers thought that membrane protein are not major players in the eradication process. It might become the major factor permitting the surrogates to enter the membranes complexes [31]. For gram positive as well as for gram-negative bacteria. It seems that the way to the top is not so clear [32].

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