

# The Antimicrobial Peptides: Ready for Clinical Trials?



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## Abstract

Bringing the antimicrobial peptides, AMPs, in pharmaceutical business was a long process with many technical hurdles after their discovery more than 30 years ago. Structure, classification and mode of action of the AMPs as well as the selection of AMPs for clinical use are discussed. The preclinical and clinical trial results in phase 1 and phase 2 studies are discussed for 9 AMPs. These results are encouraging for the future of the AMPs as alternative antibiotics.

**Abbreviations:** AMPs: Antimicrobial Peptides; LPS: Lipopolysaccharides; MIC: Minimum Inhibitory Concentration; MDR: Multidrug Resistance; CFDA: China Food and Drug Administration; IDRs: Innate Defense Regulators

## Introduction

Antimicrobial peptides (AMPs) are short proteins with antimicrobial activity. A large portion of known AMPs originate from insects. AMPs from insects represent a potential source of alternative antibiotics in the face of rising antibiotic resistance. AMPs can act against bacteria, viruses, fungi or parasites. In insects they contribute to host innate immunity [1-4]. The first AMP was extracted in 1980 from the pupae of the giant silk moths and its bactericidal properties were demonstrated for the first time [5]. Now more than 1500 AMPs have been identified in different organisms including plants, fungi, bacteria and animals. Insects are the primary source of AMPs. In traditional Chinese medicine over 1700 medicines have been produced from circa 300 insect species [6]. Difficulties in species identification, drug toxicity, development costs and large scale production slow the development of insect products into potential modern medicines [7].

## Structure and Classification

The increasing number of published insect genomes and transcription datasets combined with the ability to probe hemolymph samples directly using proteomics techniques has resulted in the discovery of many new AMPs in the past few years [8,9]. Novel AMPs can be identified by homology to known peptides, but also by other features such as the presence of protease cleavage sites and expression profiles that focus on immunocompetent cells and tissues [10,11].

Insect AMPs can be classified according to their structure or function. The three major structural classes are linear alpha-helical peptides without cysteine residues, peptides with a beta-sheet globular structure stabilized by intra-molecular disulfide bridges

and peptides that contain unusually high numbers of specific amino acid residues such as proline or glycine [1,12,13].

Cecropin is the prototype of alpha-helical linear AMP [5]. It is active against gram-negative bacteria as *Escherichia coli*. Other cecropins have been identified recently as well as cecropin-like peptides as sarcotoxins, hyaphyncin and enbocin, which can act synergistically against both gram-negative and gram-positive bacteria [14]. Defensins are the prototype of the second major structural class of insect AMPs. They have the predominantly beta-sheet globular structure. Most insect defensins act against gram-positive bacteria. Some inhibit gram-negative bacteria [15].

The third structural group are the proline-rich AMPs. Examples of these are the drosocins, lebecins, metchnikowins and apidaecins. They are divided in short-chain (fewer than 20 proline residues) or long-chain (more than 20 proline residues) AMPs. The former are more potent against gram-negative bacteria whereas the latter are more active against gram-positive bacteria and fungi [16,17]. Such differences in their specificity may be mediated by their distinct lipopolysaccharide binding activity or their ability to penetrate bacterial membranes [18,19]. The attacins and gloverins belong also to the third structural group and form the glycine-rich AMPs. Attacin from *Hylophora cecropia* inhibits outer membrane synthesis in *E. coli* whereas from *Manida sexta* binds to Gram-positive membrane liposaccharides [20-22].

## Mode of Action

Most AMPs are cationic molecules which perturb the target cells through the formation of ion channels or transmembrane pores and in this way destroy the bacterial cell [23,24]. The main targets

of AMPs are lipids in cell membranes. The AMPs bind to anionic phospholipids and phosphate groups of lipopolysaccharides (LPS) of gram-negative bacteria as well to teichoic acid and lipoteichoic acids composing the peptoglycan layer of gram-positive bacteria. The peptide anchors in the cytoplasmic membrane of the microorganism and changes the membrane structure which facilitates the incorporation into the phospholipid dual layer of the cytoplasmic membrane [25]. After adsorption into the membrane surface AMP can induce a variety of membrane perturbations within tens of nanoseconds [26].

For most AMPs an early event is the formation of hydrogen bonds between the basic residues (eg. arginine and lysine) and the phosphate groups of the lipids. Both arginine and lysine are hydrogen bond donors. However, arginine can form more stable bidentate hydrogen bonds with phosphate groups. Hydrophobic residues can further penetrate and disorganize the lipid tail region of the membrane. As more AMPs accumulate at the membrane-water interface the membrane becomes thin [27]. Membrane thinning results in lateral expansion affecting the mechanical properties of the membrane and the electrostatic properties ultimately leading to cell death. This is the pore or toroidal model. Currently 4 different models of possible actions of AMPs on bacterial cell membranes are described. Beside the toroidal model the second model is called the carpet model. In this model the AMPs cover the cell membrane in a carpet-like manner. This action requires high AMPs concentrations and causes cell membrane dissolution, similar to the action of a detergent. An example of AMPs acting in this way are the cecropins.

The third model for AMPs action is the "barrel-stave" model, in which peptides bind to the cell membrane and insert themselves into the hydrophobic core of the membrane, forming a pore and causing a leakage of cytoplasmic material and a decrease in membrane potential. In this way membrane damaging peptides such as gramicidin, finally kill the cell. The fourth and the last strategy is the destruction of cell membranes by creating "unstructured ring pores" ie. aggregate channels [23,25]. Apart from the membrane destruction some AMPs like pyrrolicin, drosocin and apidaecin may exert antibacterial activity by interactions with intracellular targets thus disrupting intracellular processes. These belong to the short proline-rich AMPs.

At first the peptides permeate and traverse the outer membrane and enter the periplasmic space. Then the process looks for the stereospecific and irreversible translocation into the cytoplasm of the bacterial cell. Inside the cell they interact with the target which is mainly the 70kDa heat shock protein DnaK. They can also interfere with DNA and RNA synthesis and have been shown to target *E. coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* [28]. Because of the contribution of electrostatic interactions binding of AMPs to microbial membranes is significant while binding of AMPs to the neutral phosphatidylcholine/cholesterol sphingomyelin-rich surfaces of animal plasma membranes is weaker. AMPs can dissipate the electrochemical gradient across microbial plasma membranes within a few seconds of addition [29,30].

AMPs must be able to rapidly pass through the thick protoglycan layer of Gram-positive bacteria and the outer lipopolysaccharide (LPS) layer of gram-negative bacteria to reach the cytosolic inner membrane. Permeation of larger markers including dye markers, metabolites and cytosolic proteins through the cytoplasmic membrane occurs on the time scale of minutes to ten minutes [29]. After an hour or more in contact with AMPs gross disruption of microbial membrane structure and morphology is often noted including blebbing, vesiculation, fragmentation, release of DNA, cell aggregation and cell death. This is in sharp contrast to conventional antibiotics which are largely bacteriostatic and need hours to days to exert their effects.

### Therapeutic Potentials of AMPs

Due to complex and multitarget mechanisms of action AMPs are distinguishable from conventional antibiotics and make them an ideal candidate to generate new antibiotics [31]. They have synergistic effects with conventional antibiotics, relatively small size, neutralizing endotoxin ability, considerable low minimum inhibitory concentration (MIC) and show that they are highly prone to kill bacteria. They have potent activity against biofilms too which also showed resistance to traditional antibiotics. In addition, AMPs have shown a wide range of antiviral properties *in vitro* [32].

In malignant cancer cells multidrug resistance (MDR) is a major mechanism of drug resistance. Few AMPs displayed cytotoxicity against MDR cancer cells. They were able to kill cancer cells rapidly, had lower side effects with easier absorption [33]. For their therapeutic use in cancer they are mandatory to perform specific anticancer activity alongside stability in serum [34,35]. A better understanding in this area would definitely contribute to cancer research.

### Selecting AMPs for Clinical Use

Bringing emerging peptides in the pharmaceutical business is a long way with many hurdles [36]. It is not surprising that the AMPs are no exception in this way. Despite the advantages of AMPs progress to date in developing them for clinical use has been disappointing. The main advance has been with vertebrate AMPs for use in topical applications and a few AMPs have entered clinical trials [7,13,37,38]. These AMPs were designed for a number of external uses as skin care, acne, eye infections and catheter-related pathogens. There have been a number of reasons for the slow progress in AMPs becoming available for clinical use. Lack of interest by large pharmaceutical companies in antibiotics for more than 30 years. Small niche biopharma companies are taking the lead fortunately.

High production costs have always been a major hurdle to the development of the AMPs since they only occur at low concentrations and the cost of solid phase synthesis is very high. Truncated synthetic AMP analogues can be produced at cheaper costs [36]. Recombinant technology had to be modified because of the antibacterial activity of the AMPs and their proteolytic degradation during production. Recent studies however have used cost effective modified recombinant techniques with *E. coli* or with the methylotrophic yeast *Pichia pastoris* as vectors to produce fully

functional insect cecropins capable of killing a range of bacteria, including MRSA [39-41].

There are also concerns about the stability and toxicity towards mammalian cells [42,43]. With amino acid substitutions, sequence splicing and changes in ratios of hydrophobic amino acids now truncated designer compounds can be produced that are effective at very low MICs [44]. Regarding development of resistance of bacteria to AMPs this was thought to be less likely to occur than with conventional antibiotics as AMPs have multiple sites of action within the bacterial cell and involve fundamental changes in the membranes. However, resistance has been described, including resistance to insect melittin and cecropin, probably due to continual selection in the laboratory. Conditions in nature are very different [45-49].

### Amps in Preclinical and Clinical Trials

In the last 30 years continuous efforts have been made to develop AMPs as clinically useful antimicrobials. To date no designed AMP antibiotics have yet reached the clinic. A number of AMPs and AMP derivatives are already at the preclinical stage and in clinical trials.

PL-5 is an alpha helical AMP and is developed by Prote Light Pharmaceuticals and has recently obtained approval from the China Food and Drug Administration (CFDA) to enter clinical trials for skin infections. PL-5 is the first AMP to enter the clinical stage in China. PL-5 is a low toxicity and highly potent AMP against a broad spectrum of drug-resistant bacteria. In addition PL-5 is able to synergize with conventional antibiotics to improve antibacterial activity in vitro and in vivo against both Gram-positive and Gram-negative bacteria. This may help or delay the emergence of antibiotic resistance [50].

POL 7080 is a synthetic cyclic peptide derived from protegin 1. POL 7080 is active against Gram-negative and Gram-positive bacteria and works by inhibiting a homolog of the beta-barrel protein LptD. LptD is an outer membrane protein widely distributed in Gram-negative bacteria that functions the assembly of LPS in the outer membrane. POL 7080 is highly active on a broad panel of clinical isolates including multi-drug resistant *Pseudomonas* with outstanding in vivo efficacy in septicemia, lung and thigh models. (Polyphar) POL 7080 is developed by Polyphar Ltd. and has completed a phase 1 trial with its partner Roche. POL 7080 has also completed a phase 2 trial in 20 patients with exacerbations of non-cystic fibrosis bronchiectasis in 2015 [51]. To date the structure of POL 7080 has not been revealed.

DPK 060 is a cationic peptide that has recently completed a phase 2 study of topical application for atopic dermatitis. DPK 060 is a broad spectrum cationic peptide active against both Gram-positive and Gram-negative bacteria. Similar to other AMPs DPK 060 is also membrane targeting [52]. DPK 060 is developed by Pergamum AB. The results of a phase 2 clinical trial of DPK 060 in outer ear infections showed a statistically significant improvement in a 10 day cure rate compared to placebo and that DPK 060 is safe and tolerable [53]. Pergamum AB has also developed LL-37, a human cathelicidin subunit. LL-37 is active against both Gram-

negative and Gram-positive bacteria. LL-37 is developed for the treatment of chronic leg ulcers. The clinical phase results show that LL-37 has a significant improved healing rate compared to placebo [53].

### Innate Defense Regulators (IDRs)

IDRs are a novel class of synthetic peptides that enhance the control of microbial infections. IDRs do not impact the adaptive immune system and do not interfere with chemotherapy, radiation or antibiotic treatments. Disquietude is a fully synthetic 5-amino acid peptide derived from indolizidine with high aqueous solubility and stability. SGX 942 (Soligenix) has broad spectrum activity against Gram-negative and Gram-positive bacteria and complements the actions of standard care antibiotics [54]. SGX 942 was first developed by Inimex and is currently pursued in a phase 2 trial by Soligenix as a treatment for oral mucositis [51]. SGX 942 has been awarded Fast Track designation from the FDA for the treatment of oral mucositis as a result of radiation and/or chemotherapy in head and neck cancer patients.

Brilacidin is a small molecule arylamide- mimic of AMPs that shows potent antimicrobial activity against a wide range of multidrug-resistant Gram-negative and Gram-positive bacteria. Brilacidin was first developed by Polymedix, Inc. and is now purchased by Cellceutix Corp. Brilacidin has completed phase 2a and phase 2b trials for the treatment of acute *S. aureus* skin infections. Similar to other AMPs brilacidin is a membrane targeting antimicrobial. It causes membrane disruption and shows efficacy in a MRSA keratitis model when applied topically; Brilacidin is equally effective as daptomycin and vancomycin [55].

Cellceutix is also developing CTIX 1278 (structure not revealed) a defensin- mimetic compound against the drug resistant superbug *Klebsiella pneumoniae*. CTIX 1278 is efficacious in a thigh burden study in a mouse model. The results are encouraging as CTIX 1278 shows similar efficacy compared to carbapenem. 6 LTX 109 is developed by Lytix Biopharma which focus on topical treatment of skin infections and nasal eradication of *S. aureus*. LTX 109 is a synthetic antimicrobial peptide mimetic which has completed phase 2 trials for the treatment of impetigo. LTX 109 is active against a broad range of bacteria including *E. coli* and *S. aureus*. LTX 109 is also active against a panel of drug resistant Gram-positive bacteria such as MRSA, vancomycin-intermediate resistant, daptomycin resistant and linezolid resistant strains [56].

Exeporfinium chloride (XF 73) is a synthetic diatonic porphyrin derivative being developed by Destiny Pharma, Brighton, UK. It has been evaluated in phase 1-2 trials for the prevention of post-surgical nasal staphylococcal infections. XF 73 is a photosensitizer that has broad spectrum activity against Gram-positive and Gram-negative bacteria and *Candida albicans* [57]. Similar to AMPs interaction of XF 73 with the cytoplasmic membrane of *S. aureus* is lethal. XF 73 showed no drug resistance for 4 common MRSA strains.

### Conclusion

The research of the antimicrobial peptides, AMPs, has been very slow in the more than 30 years since their discovery. In the face of multidrug resistance to conventional antibiotics they have

the potential to be an outstanding alternative. Lack of interest and responsibility of the large pharmaceutical companies, the high production costs and concerns about unknown safety and toxicity of oral administration, delay the introduction in clinical use. Small niche biopharma companies fortunately take the lead. At least the AMPs are now in the stage of phase 1 and phase 2 trials for topical applications as skin infections, chronic leg ulcers, wound infections and ear and eye infections. These results are discussed. and they show the future of the AMPs is still bright.

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