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New horizons for host defense peptides and lantibiotics

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Abstract

Antimicrobial peptides from either microbial sources, or based on host defense peptides (HDPs) from higher organisms, show promising activity against human pathogens. Lantibiotics have been extensively engineered by either molecular biology approaches or chemistry and both natural and modified entities have been shown to have good efficacy in animal models of infection. Amongst HDPs either truncated peptides or non-peptide mimetic molecules show substantial promise both for their direct antibiotic action and also modulation of host functions. Members of both classes have reached clinical development for therapy of systemic infections and *Clostridium difficile* infection of the gastrointestinal tract.

Introduction

The rise of antibiotic resistance in bacteria causing serious infections has led to a search for new classes of antibiotics to which resistance is not widespread and does not develop rapidly. One class which has been of considerable interest is host defense peptides (HDPs), also commonly referred to as antimicrobial peptides. HDPs represent a large class of multi-functional molecules and over 1900 sequences are reported in the Antimicrobial Peptide Database (<http://aps.unmc.edu/AP/main.php>). HDPs serve as the first line of defense against microbes for many species including bacteria, fungi, plants, insects, worms and mammals, and their direct antimicrobial activities originate at membrane targets which cannot mutate rapidly to evade antibiotic action. Furthermore their mode-of-action often involves multiple targets as well as potentially beneficial interactions with the host immune system which may complement their direct antibacterial activity. Despite these promising attributes, development to date has been mostly for topical applications. However, in the last two to three years, members of several classes of antimicrobial peptides including lantibiotics, peptidic derivatives and non-peptidic mimics have progressed towards clinical evaluation for treatment of life-threatening infections. This review discusses recent developments with an emphasis on the potential of these agents to have the desired pharmacokinetics, tissue distribution, safety and tolerability for use in medicine.

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Host defense peptides; Overview

HDPs are typically 12 to 50 amino acid residues in length and generally adopt either α -helical or cysteine-rich beta-sheet conformations [1]. There is little conservation in the primary amino acid sequences between HDPs but their physiochemical properties are remarkably similar. All adopt an amphiphilic architecture with positively charged groups segregated to one side of the protein scaffold and hydrophobic groups on the opposite surface and this facial amphiphilicity appears to be responsible for their biological activity. There are several mechanisms proposed for the direct killing activity, involving both membrane and non-membrane effects [2], which are mediated initially by an ionic interaction between the positively charged peptide and negatively charged phospholipids and polysaccharides of bacterial membranes. Mammalian membranes are spared because of their distinct composition that includes primarily zwitterionic phospholipids which present a net neutral surface charge and cholesterol which increases membrane density [1,3].

Several classes of HDPs have also been found to possess immune modulatory and anti-inflammatory activities which can be important in infection control, barrier function maintenance and wound healing [4]. The human α and β defensins, families of small β -sheet peptides, are chemotactic for neutrophils, monocytes and dendritic cells and induce expression of several phagocyte chemokines in epidermal keratinocytes [5,6]. HDPs also help balance inflammatory activities during an infection response by modulating cytokine production and binding to proinflammatory bacterial components, such as lipopolysaccharide (LPS) and lipoteichoic acid (LTA), preventing interaction with their targets, the Toll-like receptors, Toll4 and Toll2, respectively [7,8].

Importantly, the membrane activity of the HDPs has been associated with a low frequency for resistance development presumably related to the complex changes in membrane structure that would be required to evade the action of the HDPs and their “multi-hit” properties that include both membrane and intracellular targets [2]. Some organisms are able to survive in an environment rich in HDPs (i.e. enteric organisms of the gastrointestinal tract) by mounting certain retaliatory responses, including production of proteolytic enzymes that degrade the peptides [9] and activation of two and three component signaling pathways that reduce the net negative charge on the bacterial membrane surface [10,11]. Under normal conditions, balance of the host microbiome is maintained with HDPs appearing to play a key role in achieving this balance through their direct antimicrobial activities, and ability to modulate the innate immune system and mucosal barrier. Their importance in this regard is underscored by the correlation in expression level deficiencies of the human α -defensins HD5 and HD6 with severity of Crohn's disease [12], an inflammatory bowel condition marked by invasion of the luminal microbes into the intestinal epithelia.

Therapeutic use; Peptides and peptidic derivatives

Several HDP-like peptides have long been used as topical medicines (polymyxin B and gramicidin S). Recently, the parenteral use of polymyxin B for treatment of severe Gram-negative infections has increased substantially, despite its tenuous safety profile, due to the emergence of highly drug resistant pathogens [13]. Given their broad activity profiles, amphiphilic HDPs appear to be ideal therapeutic agents, however, significant pharmaceutical issues, including poor tissue distribution, systemic toxicity and difficulty and expense of manufacturing, have severely hampered their clinical progress. Several strategies, such as substitution of D- amino acids for the normally occurring L-isomers [14] and creation of amphiphilic helices with β -peptides [15,16] or peptoids [17] have created molecules with potent activity and improved stability against proteolytic degradation. Due to poor pharmacokinetic and pharmacodynamic properties often encountered with peptides and

complex toxicity issues associated with direct cellular damage and immune-related responses, clinical development of the peptides (or their derivatives) focused on topical applications. Initial clinical studies performed over the past decade evaluated pexiganan for infections associated with diabetic foot ulcers, omiganan for catheter-related infections and burn wounds, and iseganan for oral mucositis [18]. All of these efforts were unsuccessful for a variety of reasons including lack of efficacy over standard of care practices, trial design and manufacturing limitations. However, there are several preclinical and clinical programs with HDP derivatives that display particular promise. A lipohexapeptide, HB1345, possesses both antimicrobial and anti-inflammatory activities suitable for the treatment of acne [19]. A plectasin-derived peptide, NZ2114, demonstrates potent activity against Gram-positive pathogens and is systemically active against MRSA and *S. pneumoniae* in animal models of bacterial infection [20,21]. An alternate approach separating two cationic amino acids with a flexible acyl backbone, referred to as oligomers of acylated lysine (OAKs) enables fine control over the molecular hydrophobicity by changing the acyl chain length while not limiting the rotational freedom around the peptide axis into any particular secondary structure. The OAKs demonstrate rapid bactericidal activities, low incidence of resistance development and activity in animal models of bacterial infection [22,23]. The antimicrobial peptide hLF1-11, the N-terminal 11 amino acid portion of lactoferrin, demonstrates potent antimicrobial activity *in vitro* and *in vivo* [24,25] and enhances the inflammatory response of monocytes and directs monocyte-macrophage differentiation toward cells with enhanced antimicrobial properties [26,27]. hLF1-11 is being developed for the treatment of bacterial and fungal infections in patients receiving hematopoietic stem cell transplantations [28]. Interestingly, synthetic cationic peptides that are designed to modulate the innate immune system (innate defense regulators or IDRs) and are devoid of direct antimicrobial activities have been shown to have significant efficacy in animal models of systemic infections caused by Gram-negative and Gram-positive bacteria [29]. These IDR peptides appear to act, at least in part, through recruitment of monocytes and their clinical development may be as adjuncts to other antibiotic therapies to enhance efficacy and safety [30].

Therapeutic use; nonpeptidic mimics

A series of non-peptidic mimics of the HDPs have been developed that have distinct advantages over peptides for pharmaceutical uses. The approach is to capture the structural and biological properties of HDPs within the framework of inexpensive oligomers (see Figure 1).

Small synthetic oligomers that adopt amphiphilic structures while exhibiting potent and selective antimicrobial activity would be less expensive to produce, have better tissue distribution, and be much easier to fine-tune structurally to improve activity and minimize toxicity. Aromatic arylamides [31], phenylene ethynylenes [32] and N,N'-linked oligoureas [33,34] are easily synthesized and provide chemically accessible attachment points for addition of side groups to regulate the overall structure of the molecules. Interestingly, many of the structure – activity relationships described for HDPs translate to the small oligomers, but for each scaffold there is a delicate balance between charge, hydrophobicity and rigidity that must be fine-tuned to optimize both potency and selectivity [35]. For the arylamide oligomers, stabilization of an amphiphilic structure is associated with an increase in potency [36,37] whereas scaffold flexibility is needed for optimal activity with the OAKs [23]. The cidal activity of the arylamide oligomers is mediated through interactions at the bacterial cell membrane [38] and lead arylamides are robustly active in animal models of bacterial infection [37]. The clinical lead compound, PMX30063, is currently in Phase 2 clinical trials as an intravenous (IV) anti-staphylococcal agent for treating Acute Bacteria Skin and Skin Structure Infections (ABSSSI).

In addition to the translation of the direct antimicrobial activity of HDPs to small nonpeptidic scaffolds, initial results indicate that immune modulatory activities can also be conferred by these HDP mimics. A small phenylalkyne mimic, mPE (MW 520), with potent and broad bactericidal activity also potently inhibited the IL-1 β -induced secretion of IL-8 in gingival epithelial cells and THP-1 cells which was also associated with a reduction in the activation of NF- κ B, [39]. Therefore, like some of the peptidic derivatives, HDP mimics can act as a direct antimicrobial and anti-inflammatory agent in infected tissues. This dual activity on a small nonpeptidic framework opens a promising area of investigation for developing new therapeutic agents that could be highly effective in treating a wide array of disorders that possess both microbial and inflammatory components, including, but not limited to, periodontitis, oral and vaginal candidiasis, oral mucositis, inflammatory bowel disease, acne and atopic dermatitis.

Lantibiotics; Mode-of-action and *in vitro* activity

Lantibiotics are a group of ribosomally synthesized, post-translationally modified antimicrobial peptides containing unusual amino acids, such as dehydrated and lanthionine residues. Although the frequent discovery of newer agents has led to regular review and updating, the classical scheme of Jung, dividing lantibiotics into three classes based on structure and mode-of action, is still of value [40]. Class A lantibiotics, typified by nisin, are rod-like in overall shape and have two active domains. One domain of the molecule binds to the cell wall biosynthetic intermediate lipid II and the other is involved in disruption of membrane structure. Whereas the dominant antibacterial mechanism of the Class A lantibiotics is their membrane-disruptive effect, Class B lantibiotics such as mersacidin (MRSA-cidin) have solely a lipid II binding domain and act predominantly as inhibitors of cell wall biosynthesis. A third class of two-component lantibiotics replicates the two domain action of the Class A lantibiotics, but utilising two separate synergistically acting peptides.

Although lantibiotics have been in use for many years as food-preserving agents, the rise of multi-drug resistant bacterial infections has led to a re-evaluation of their potential for use against life-threatening infections [41]. Lantibiotics of both class A and class B have been shown to have promising activities against key pathogens such as MRSA, *Streptococcus pneumoniae* and *Enterococcus faecalis*, and to have no cross-resistance against other major classes of antibiotics in use today.

Lantibiotics are generally considered to be narrow-spectrum agents with activity against only Gram-positive pathogens, however, other cationic membrane disrupting peptides have broad-spectrum activity and there is no *a priori* reason why the activity of lantibiotics should be restricted to Gram-positive bacteria. Indeed some variants of nisin are reported to have appreciable anti-Gram-negative activity [42]. Recently a lantibiotic from *Bifidobacterium longum*, although not fully characterised, has been reported to have broad-spectrum activity [43].

Structure-activity relationships of lantibiotics

Although outside the scope of this review a large body of work on the biosynthesis of lantibiotics has supported the systematic generation of mutants, some of which have improved antibacterial activity and other pharmaceutical properties [44]. In addition there have been impressive developments in the total chemical synthesis of lantibiotics which open up further opportunities for manipulation [45].

***In-vivo* evaluation of lantibiotics as systemic antibacterials**

Although the activity of lantibiotics *in vitro* has long been recognised, there has been a recent increase in studies aimed at evaluating lantibiotics as systemic antibiotics. The peptidic nature of the molecules raises questions about their stability in the systemic circulation and tissue penetration, whereas the mode of action of type A lantibiotics at least, as membrane disrupters, has led to questions about selectivity for microbial membranes over mammalian membranes and hence safety and tolerability. These questions are beginning to be addressed as agents are being brought forward towards clinical evaluation.

Nisin has been investigated as a systemic antibacterial since as early as 1952 when it was shown to be effective in mice infected with *Mycobacterium tuberculosis*, *Streptococcus pyogenes* and *Staphylococcus aureus* [46]. Later nisin was shown to be more effective than vancomycin in a *S. pneumoniae* murine infection model [47]. However, nisin is known to be proteolytically labile and is cleared from the systemic circulation with a half-life of 0.9h in mice.

Other type A lantibiotics, the mutacins, may be more stable to proteolysis than nisin. Mutacin B-Ny266 was effective in a murine model of disseminated *S. aureus* infection when injected intraperitoneally [48]. More extensive studies have been carried out with MU1140 which is reported to be in preclinical development by Oni Biopharma Inc. MU1140 is extensively serum bound (93%) causing a reduction of activity vs. *S. pneumoniae*, but surprisingly, serum potentiates activity against *S. aureus* [49]. In rats MU1140 was found to undergo a rapid distribution phase followed by elimination with an overall terminal half-life of 1.6h [50]. The volume of distribution was quite high for a large molecule at 2.2 – 3.5L/kg. These PK parameters together with *in-vitro* pharmacodynamic studies have been used to develop a PK/PD model which predicted that T>MIC should correlate with efficacy with a T>MIC of 25% sufficient to achieve a maximal therapeutic effect [50,51]. MU1140 was not well-tolerated after rapid injection. A 'hypersensitivity' reaction was observed within 5 min of dosing which could be prevented by administration of the anti-histamine diphenhydramine. The response was compared to 'red man syndrome' which occurs after rapid administration of a number of antibiotics, especially vancomycin, and can be minimised by slow infusion [52].

The epidermin-related lantibiotic, NAI-107 (microbisporicin), has potent *in-vitro* antibacterial activity against staphylococci, streptococci and enterococci as well as some fastidious Gram-negative bacteria (D Jabes *et al.*, abstract F1-1502, 49th Intersci. Conf. Antimicrob. Agents Chemother, San Francisco, September 2009). NAI-107 was highly effective in an acute lethal infection model against a GISA strain of *S. aureus*, two VRE strains and *S. pneumoniae* with ED₅₀ values comparable to or lower than vancomycin or linezolid [53]. The pharmacodynamics of the molecule were investigated more fully in a rat granuloma pouch model and in a rat model of endocarditis (*S. aureus*) where a profound reduction in bacterial counts in the heart vegetation was achieved at 20mg/kg *bid*. The response was superior to that seen with vancomycin at 100mg/kg *bid*. As with MU1140, NAI-107 underwent high serum binding (>90%). NAI-107 is reported to be in preclinical development with NAICONs/Sentinella Pharmaceuticals.

Although having only moderate MIC values the type B lantibiotics, mersacidin and actagardine, also have impressive efficacy in animal models of infection against staphylococci and streptococci [54,55]. Some derivatives of actagardine have been claimed to have improved activity [56].

Activity of lantibiotics against *Clostridium difficile*

Lantibiotics such as lacticin 3147 have good activity against the Gram-positive spore-former *C. difficile* *in vitro* [57]. However, use in the GI tract presents a tough challenge for a peptidic agent; neither lacticin 3147 nor nisin survive for extended periods in the intestinal environment [58,59]. In contrast the type B lantibiotic, NVB302, is stable in the GI tract and efficacious in a hamster cecitis model (AN Appleyard *et al.*, abstract F1-1520, 49th Intersci. Conf. Antimicrob. Agents Chemother., San Francisco, September 2009). It also has selective activity for *C. difficile* over the predominantly Gram-negative normal gut flora (SN Wadman *et al.* abstract F1-1518, 49th Intersci. Conf. Antimicrob. Agents Chemother., San Francisco, September 2009) leading to resolution of a simulated infection in an *in vitro* human gut model with less disruption of the *Bacteroides fragilis* group in comparison with vancomycin (Huscroft GS *et al.*, abstract F1-1607, 50th Intersci. Conf. Antimicrob. Agents Chemother., Boston, September 2010). NVB302 has entered clinical development with Novacta Biosystems Limited.

Conclusions and future perspectives

The challenge of developing antimicrobial peptides into therapeutics for serious bacterial infections is now undoubtedly being addressed. Serious attention is now being paid to generation of drug-like entities which can be produced to the required quality standards and at a commercially viable cost of goods. As well as antibacterial activity, tissue distribution, pharmacokinetics and safety are for the first time being addressed systematically in *in vivo* models and clinical trials. In the next 2–3 years several agents are likely to undergo thorough clinical evaluation for the treatment of serious infections and the true potential of this class will be ascertained.

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Highlights

- We review recent developments in therapeutic application of antimicrobial peptides
- Host defense peptides (HDPs) may combine antibiotic with host modification activity
- Some HDPs and lantibiotics have promising activity in systemic infection models
- HDPs and non peptidic mimics are in clinical trials for systemic infections
- Lantibiotics are in clinical trials for *C. difficile* infection

Figure 1.

Conceptual design of HDP mimics.

Left panel: Amphiphilic structure of magainin 2; cationic groups in blue, nonpolar groups in green and the peptide backbone in yellow. **Right panel:** *de novo* designed HDP mimics which capture the facially amphiphilic architecture and critical physicochemical properties needed to establish robust antimicrobial activity.