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Overview of Host Defense Peptides and Their Applications for Plastic and Reconstructive Surgeons

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Short Running Head: Host Defense Peptides
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Abstract:

Host defense peptides (HDPs) are a family of endogenous short peptides that are found in all living beings and play a critical role in innate immunity against infection. In addition to their direct antimicrobial actions against pathogens, including multi-drug resistant bacteria, they also demonstrate important functions in immunomodulation, tumor cell lysis, and tissue regeneration. These properties have made them a topic of clinical interest for plastic surgeons because of their potential applications as novel antibiotics, wound healing medications, and cancer therapies. The rising clinical interest has led to a robust body of literature describing HDPs in great depth and breadth. Numerous mechanisms have been observed to explain their diverse functions, which rely on specific structural characteristics. However, these peptides remain mostly experimental, with limited translation to actual practice due to numerous failures to achieve acceptable results in clinical studies. Despite the broad ranging potential of these peptides for use in the field of Plastic and Reconstructive Surgery, they are rarely discussed in our literature or at our scientific meetings. In this review, we provide a summary of the background, structure, function, bacterial resistance, and clinical applications of HDPs with the goal of stimulating HDP-based innovation within our field.
**Background**

The human immune system is comprised of the innate and the adaptive immune systems working synergistically to combat infectious agents. Host defense peptides (HDPs) are endogenous short peptide compounds that are recognized as a critical component of the innate immune system and are found in epithelial barriers and circulating leukocytes. The first evidence of host defense peptides emerged in the late 1800's when human secretions were discovered to possess antimicrobial properties.\(^1\) To date, there are over 2800 known host defense peptides.\(^2\) It is now believed that HDPs are expressed ubiquitously across all species and exist in nearly every organism including mammals, insects, fish, amphibians, prokaryotes, archaea (non-bacterial prokaryotic organisms), and even viruses.\(^3\) Figure 1 provides a timeline of important HDP discoveries including isolated compounds and species of origin.

An extensive amount of basic science and clinical research has been performed to define the role of HDPs in host immunity. Original descriptions referred to these compounds as "antimicrobial peptides" or "AMP's" based on the theory that their principal purpose was the direct eradication of bacterial species. However, recent studies have revealed that host defense peptides are capable of eliminating bacteria, viruses, parasites, and even archaea\(^4,5\) and these peptides have displayed critical functions in immunomodulation and wound healing that may actually be more important than their direct actions against infectious agents.\(^6,7\)
Structurally and mechanistically, host defense peptides are a diverse class of molecules that can be synthesized through a multi-enzymatic process or ribosomal translation, with or without post-translational modification.\(^8\) Host defense peptides are therefore classified into subtypes based on molecular similarity, with Cathelicidins and Defensins, the two most studied HDP families in humans. The only known human cathelicidin is LL-37, the 37 amino acid C-terminal domain of the pro-peptide hCAP18.\(^9\)\(^-\)\(^11\) Defensins are similarly important for human host defense, but there are numerous compounds in this class, which are further categorized as \(\alpha\)-, \(\beta\)-, and \(\theta\)-defensins based on structure (Figure 2). This sequence and structural diversity allows the defensin class of peptides to perform a breadth of important functions in human defense and immunomodulation.

HDPs have generated substantial clinical interest due to their ability to eradicate diverse classes of virulent organisms, including fastidious multi-drug resistant bacterial strains.\(^12\)\(^,\)\(^13\) Technologies based on these peptides have the potential to revolutionize the practice of plastic surgery, incorporating elements of infection prevention, tumor extirpation, regeneration, wound care, and immunomodulation.

In this overview, we provide a summary of the scientific attributes of host defense peptides including their molecular structures, various biologic properties and respective mechanisms of action, and bacterial resistance methods. We additionally provide some overview of the different synthetic variants of host defense peptides and how they affect the molecular
properties, as well as attempted clinical applications across all specialties with a focus on plastic and reconstructive surgery. Our intent is to present the many capabilities of host defense peptides and relevant synthetic modifications along with some of the most notable examples of clinical studies with HDP compounds to provide readers with a background so that they may consider new applications that may advance the field of Plastic and Reconstructive Surgery.

**Structure**

Host defense peptides are a structurally heterogeneous category of molecules. Despite the significant sequence diversity, there are some characteristic features which are typically conserved throughout HDP peptides. In general, all HDPs are composed of short amino-acid chains with both cationic and hydrophobic moieties which are crucial for activity and intimately related to the proposed mechanisms of action. The hydrophobic domains are considered essential to the anti-bacterial efficacy of the peptides, with several studies demonstrating loss of function in the absence of hydrophobic residues (Figure 3).^{14-16}

In order to organize the understanding of these complex molecules, host defense peptides are typically classified into categories based on structural features (Figure 4). No official structural classification system has been universally adopted, so the existing classification systems reported in the literature are relatively inconsistent. We describe one of the most
commonly cited classification systems including a list of common HDPs (Table 1).

Within this organizational paradigm, the first group is defined by short linear peptides that form α-helices (Figure 4). The prototypical example from this class is the aforementioned heavily-studied human cathelicidin, LL-37. However, this classical description has become clouded as further research has demonstrated that many of these short peptides adopt amorphous inconsistent secondary structures in aqueous solution, but conform to an α-helix selectively in the presence of detergents like trifluoroethanol or sodium dodecyl sulfate. In particular, it has been shown that these compounds appear to become α-helices as they penetrate amphiphilic bacterial membranes, which is important for their antimicrobial activity.

The second major structural group of HDP's is defined by the lack of simple α-helices or β-sheets and the presence of several repeats of the same amino acid. These peptides often have a linear structure, although some may adopt an extended poly-proline helix (Figure 4). This group includes the bovine anti-microbial neutrophil cathelicidin, Indolicidin, which is only 13 amino acids long but contains three proline residues and five tryptophan residues.

The third structural group adopts a β-sheet secondary structure with or without disulfide links between sulfur-containing cysteine residues (Figure 4). This class includes the defensins, which are characterized by the presence of three disulfide bonds and further classified as α-, β-, or θ-
depending on the specific structure and orientation of the cysteine residues and intra-molecular disulfide bonds. The α- and β-defensins are expressed in human tissues, whereas θ-defensins are only found in non-human primates.27

The final group is the loop peptides defined by a composite loop structure (Figure 4). This family includes Buforin I, a 39 amino acid peptide cleaved from histone 2A by pepsin, which contributes to gastric antimicrobial defenses.28

In addition to the diversity of the secondary structures of HDPs, many attain further structural complexity by undergoing post-translational modification, including carboxy amidation, amino acid isomerization, halogenation, oxidation, reduction, and phosphorylation, among others. It is estimated that over half of the known HDPs undergo post-translational modification, which is often necessary for their antimicrobial activity. 29

**Mechanism**

Host defense peptides exert their multiple actions through a myriad of mechanisms. In general, these mechanisms must be specific for infectious agents and malignant cells while simultaneously sparing host tissues; importantly, HDPs have been observed to specifically differentiate infectious processes from sterile inflammation.30

*Antimicrobial*
The most commonly cited and studied mechanism of action for HDPs is bacterial membrane permeabilization, allowing entry of extracellular molecules (Figure 5). The first step involved in membrane perturbation necessitates successful identification and binding on a pathogen membrane. The numerous cationic residues within HDPs are initially attracted to the net negative charge present on most bacterial membranes. In contrast, eukaryotic cells typically have neutrally charged membrane components including phosphatidylethanolamine, phosphatidylcholine, and sphingomyelin. The lack of negative charge on animal cells effectively prevents the initial electrostatic attraction, and spares host cells from the downstream lytic actions of HDPs. However, malignant host cells tend to have higher levels of negatively-charged phosphatidylserine (PS), similar to bacterial pathogens, promoting binding of HDPs to the tumor membrane.

Once adhered to target cell membrane, most HDPs act by causing disruption of the lipid bilayer ultimately leading to cell death. Three separate membrane perturbation models have been observed: the barrel-stave, carpet, and toroidal models (Figure 2).

In the barrel-stave model, HDPs aggregate into a cylindrical pore through the membrane with each peptide acting as one of the staves. In this model, the peptides typically adopt an α-helix secondary structure with hydrophilic residues lining the inside of the pore, and the hydrophobic residues directed out towards the surrounding lipid bilayer (Table 1).
The carpet model theorizes that HDP peptides initially accumulate parallel to the plane of the target membrane, similar to a carpet. After a threshold concentration is reached, the carpet eventually disintegrates and micellizes the membrane altogether, leading to massive disruption instead of discrete pores.\textsuperscript{44}

The third model is the toroidal pore, in which the membrane bilayer is bent by embedded HDP peptides until the inner and outer layers become one continuous surface with a resulting hole. The toroidal model is supported by neutron scattering studies demonstrating a large diameter pore and rapid flipping of lipids between the two membrane bilayers.\textsuperscript{46,47}

As further research has evolved, several novel mechanisms have been introduced to explain the antimicrobial actions of HDPs. Short synthetic peptides rich in the amino acids arginine and tryptophan have been observed to embed into the target membrane and dislocate cell wall synthetic machinery, but spare the membrane itself.\textsuperscript{48} Other HDPs completely cross the target membrane without any disruption and exert entirely intracellular mechanisms of action.\textsuperscript{49} Once in the cytosol, peptides can block DNA synthesis, RNA translation, or cell wall synthesis, typically by binding the anionic DNA or RNA itself and preventing unwinding or preventing coupling with necessary cellular machinery.\textsuperscript{50-54}

\textit{Immunomodulation}
Despite the mounting mechanistic evidence of direct antimicrobial activity, there is some doubt that the bacteriocidal properties are the most important functions of HDP compounds \textit{in vivo}. LL37 demonstrates significantly reduced bacteriocidal effects in physiologic concentrations of magnesium, calcium, and sodium.\textsuperscript{57} Additionally, many HDPs display limited bacterial lysis in the presence of host cells, suggesting questionable \textit{in vivo} efficacy.\textsuperscript{58} These peptides are also often expressed in host tissues at concentrations below the minimal threshold for bacteriocidal activity.\textsuperscript{59}

Many researchers believe that the most important functions of HDPs may actually be gene regulation and immuno-modulation. LL37 can inhibit the inflammatory effects of macrophage stimulation by lipoteichoic acids (LTA).\textsuperscript{60} Similarly, LL37 is capable of binding the outer membrane lipopolysaccharides of Gram-negative bacteria to reduce the endotoxin effects on systemic inflammation, ultimately preventing sepsis in rat models.\textsuperscript{61,62} These properties are distinct from the direct antimicrobial properties, and can be modified separately with different amino acid substitutions.\textsuperscript{63} Synthetic analogs have also now been constructed without any \textit{in vitro} activity against microbes but still retain protective properties \textit{in vivo} based purely on the immuno-modulatory properties. These innate defense-regulator peptides (IDR-1) show \textit{in vivo} efficacy against several multi-drug resistant organisms including methicillin-resistant \textit{Staphylococcus aureus} (MRSA), vancomycin-resistant \textit{Enterococcus}, and \textit{Salmonella enterica}
through selective immuno-stimulation of neutrophils and monocytes while simultaneously limiting deleterious inflammatory consequences.\textsuperscript{66}

\textit{Wound Healing}

Finally, some preliminary research suggests an important role for HDP compounds in the wound healing process, which is particularly relevant to Plastic and Reconstructive Surgeons.\textsuperscript{67} Importantly, β-defensins, as well as LL37, have been implicated in the induction of keratinocyte proliferation and migration and studies demonstrate accelerated healing in a diabetic infected porcine skin wound model with application of β-defensins.\textsuperscript{68,69} Additionally, HDPs appear to help regulate angiogenesis and help stimulate vascular growth in healing tissues.\textsuperscript{70} These wound healing properties have been found to extend to multiple tissue types including intestinal and pulmonary epithelial wounds.\textsuperscript{71–74}

\textit{Resistance}

Bacterial resistance to HDPs is also an unfortunate reality that is clinically and experimentally observed.\textsuperscript{75} In fact, infectious virulence has been correlated with resistance to HDPs for many bacterial organisms.\textsuperscript{75,76} The significant diversity of HDP mechanisms requires the resistance strategies to employ equally numerous solutions based on the specific peptide and target organism (Table 2).
Clinical Applications

In order to fully capitalize on the theoretical potential of host defense peptide-based therapeutics (HDPs), substantial research efforts have been made to optimize the desired properties by modifying existing peptides and developing novel synthetic compounds. The most common synthetic methods are summarized in Table 3.

While host defense peptides may initially appear to be a reasonable therapeutic strategy for treatment of antibiotic-resistant human infectious disease, the majority of promising studies have been performed in vitro and the clinical in vivo results have been less impressive (Table 4). In particular, the issues of clinical stability, toxicity, cost, salt sensitivity, and proteolytic degradation have been considered the main barriers to ultimate clinical use.77

Topical Antimicrobial Applications

Due to concerns of toxicity and instability associated with systemic administration of HDPs, the majority of tested compounds have been introduced as topical antimicrobials. Topical agents are particularly important therapeutic agents for plastic and reconstructive surgeons who frequently manage complex wounds with polymicrobial colonization and invasive infection. One of the most famous clinical therapeutics derived from HDPs is Pexiganan, an analog of Magainin-2 from African claw frogs.78
It was developed as a topical antimicrobial specifically marketed for management of diabetic ulcers. Despite strong Phase II efficacy data, Pexiganan was not FDA approved for this indication due to a lack of significant improvement in primary clinical endpoints compared to topical ofloxacin. Pexiganan was later rebranded as Locilex by Dipexium (Now PLx Pharma, Houston TX) and again failed phase III clinical trials in 2016 by showing no difference in bacterial eradication or wound closure for diabetic lower extremity wounds. Dipexium has reports that it is currently investigating novel clinical indications for pexiganan.

Omiganan is a promising topical HDP therapy that has not been successfully translated into clinical practice. Developed by Migenix (Vancouver, Canada), Omiganan is a homolog of bovine indolicidin which was investigated for reducing central venous catheter infectious. In vitro studies demonstrated that Omiganan was capable of eliminating all organisms commonly associated with catheter infections, including multi-drug resistant strains. However, phase III clinical trials failed to improve the primary endpoint of clinically diagnosed catheter site infections, even though secondary endpoints of catheter colonization and microbiologically-confirmed catheter infections were significantly reduced. Omiganan has also demonstrated excellent potential for acne and rosacea in pre-clinical pig skin colonization models. Based on this promising data, Omiganan has entered Phase II clinical trials for acne vulgaris starting in 2015, although results have not been published yet. Similarly, a synthetic derivative of a
cecropin-like HDP found in *Helicobacter Pylori*, called HPA3NT3, has been used successfully against acne, although clinical trials are still pending.\textsuperscript{85–87} NAICONS (Milano, Italy) is also currently testing their medication, NAI-Acne (CB-06-01), for use in acne vulgaris. After licensing to Cassiopea SpA (Lainate, Italy), the drug successfully completed phase II efficacy studies with selective elimination of drug resistant *propionobacterium acnes* organisms.\textsuperscript{88}

In 2008 OctoPlus (Leiden, Netherlands) demonstrated efficacy in a Phase II clinical trial for OP-145, a 24 peptide fragment of LL37, for topical use in patients with chronic resistant otitis media.\textsuperscript{89} This compound, also called p60.4ac, is now under investigation for its role in biofilm eradication and use as a gel to prevent methicillin resistant staph aureus (MRSA) wound infections and nasal colonization.\textsuperscript{90,91} P10 is another fragment of LL37 which has proven to be effective against mupirocin-resistant MRSA strains and can neutralize endotoxins. It is currently under investigation for atopic dermatitis by Madam therapeutics (Woerdense Verlaat, Netherlands) under the market name SAAP-148.

Iseganan, derived from Protegrin-1 (porcine leukocytes), was investigated for treatment of mucositis in head and neck malignancy patients undergoing radiotherapy. Unfortunately, the results of this multi-national Phase III clinical trial published in 2004 failed to demonstrate any benefit in reduction of oral mucositis compared to the group treated with simple oral hygiene and placebo.\textsuperscript{92} It additionally failed to improve mortality rates and ventilator-associated pneumonia in critically ill intubated patients.
treated six times per day. After these trials failed to demonstrate clinical efficacy of Iseganan for these indications, Iseganan was evaluated for use in patients receiving stomatotoxic chemotherapies. The initial results from the Phase III clinical trial were very promising with an overall reduction of oral pathogens. Unfortunately, rigorous clinical endpoints were not examined. PAC-113, a 12-residue peptide based on human salivary histatins, has demonstrated efficacy in Phase II trials as a therapy for oral candidiasis in HIV patients, although clinical translation remains pending. The manufacturer, Pacgen (Vancouver, Canada), has additionally reported expanding indications for PAC-113 to include over the counter hand creams and feminine products.

HDPs may also have an important role in wound care for burn patients. It is known that severe burns cause alterations to the immune system, including impaired lymphocytic response and complement dysfunction. Reduced expression of host defensins by burned tissues likely also contributes considerably to susceptibility to infection. The application of hydrogels impregnated with an HDP in a rat burn model resulted in accelerated healing with reduced infection, inflammation, and oxidative stress. Furthermore, the use of topical epinecidin-1 in a MRSA infected porcine burn model resulted in reduced infection, accelerated healing, improved collagen architecture, and enhanced angiogenesis.

Hardware Coating
As an extension of topical antimicrobials, HDPs have been suggested as a possible coating substance for implanted hardware. This indication is particularly appealing because HDPs and related polymers have been successfully used to prevent biofilm formation, which substantially contributes to hardware infections and the resistance of those infections to systemic antimicrobial agents.\textsuperscript{100,101} Promising results were obtained using coatings based on melittin-cecropin peptides, which can be applied to a variety of surfaces and maintains its antimicrobial activity while minimizing host toxicity.\textsuperscript{102} Covalently-bound coatings of amphiphilic cationic peptides have also been demonstrated to have efficacy against several bacterial pathogens and can prevent the formation of biofilms.\textsuperscript{103} This coating strategy additionally provided a mechanical barrier to bacterial adherence by reducing platelet adhesion and protein absorption. The concept of using an HDP coating is frequently applied for orthopedic hardware with promising preclinical results.\textsuperscript{104-106}

Systemic Antibiotics

Despite a large focus on topical agents, HDP derived therapies have also been developed for systemic use. While the peptide structure limits the oral administration possibilities for many compounds, because of degradation by gastric peptidases, the observed preclinical efficacy against multi drug-resistant bacterial strains has generated significant interest in these compounds as the potential future of antibiotics.\textsuperscript{107} With systemic
administration, these compounds can also inhibit the sepsis response with resulting improvements in the mortality rates of critically ill patients.\textsuperscript{108}

In 2007 AM-Pharma (Bunnik, Netherlands) initiated clinical trials for hLF-11, an 11 amino acid fragment of lactoferrin, for preventing bacteremia and fungemia infections in immunosuppressed patients after hematopoietic stem cell transplantation.\textsuperscript{108} However, the company made a strategic decision to prematurely terminate the study before initiating patient enrollment. Plectasin is an antibiotic in the defensin family of HDPs which was initially pioneered by Novozymes (Bagværd, Denmark), with promising preclinical data against multi-drug resistant bacteria.\textsuperscript{109-111} While commercial development was halted, preclinical studies are actively ongoing with promising results.\textsuperscript{112-116} Oragenics (Tampa, FL, USA) has investigated Mutacin 1140, a lantibiotic produced by \textit{streptococcus mutans}, as a therapy for \textit{clostridium difficile}.\textsuperscript{88} They recently published efficacy of Mutacin 1140 in a hamster model with low toxicity and better potency than oral vancomycin, and are now preparing for clinical trials. Similarly, Surotomycin CB-315 (Cubist pharmaceuticals, Lexington, MA, USA) recently completed Phase III trials but failed to demonstrate superiority to vancomycin for clearing \textit{clostridium difficile}, and the drug is likely to be discontinued.\textsuperscript{117} A recombinant 21-residue fragment of bacteriocidal/permeability increasing protein, Neuprex from XOMA (Berkeley, CA, USA), was evaluated as an adjunct therapy in pediatric patients with \textit{meningococcemia} but failed phase III clinical trials.\textsuperscript{118}
Therapeutics derived from HDPs have also been investigated for use against nonbacterial infectious pathogens. Several peptides have direct anti-viral effects against strains of influenza. Specifically, retrocyclins are among the most studied HDPs for use against viral agents. *In vitro* studies have revealed that retrocyclins can inhibit viral binding to CD4 receptors, effectively preventing HIV cellular entry. Retrocyclin analogs can even protect host cells against traditionally antiviral-resistant HIV strains. Helix BioMedix (Bothell, WA, USA) was previously developing a HDP-based therapy to prevent sexually transmitted HIV and HSV, but this therapy never materialized. Despite the promising preclinical data, no clinical translation has been achieved yet for antiviral applications.

**Wound Healing**

LL37 has also been evaluated as a topical wound healing therapy, specifically for venous stasis ulcers. Wound healing was accelerated in treated patients up to six times the rate of placebo patients with no apparent safety concerns. Further, healing rates in venous stasis patients have been directly associated with serum LL-37 concentrations, suggesting LL37 as an important contributor and a possible biomarker for healing. Based on these preliminary data, novel AMP derivatives of LL-37 have been tested for diabetic or critical ischemia leg ulcers in phase I/IIa first-in-patient studies with remarkable dose-dependent improvement in healing over placebo control. While final approval has not been achieved, it is likely that AMP
products will play an increasingly important role in the management of difficult wounds encountered by Plastic and Reconstructive Surgeons in the near future.

Malignancy

Anti-cancer therapeutics is another field of growing interest for HDP-derived compounds based on the suggested role for HDPs as part of the immune system's ability to eliminate malignant tissues. Phyloseptins, magainins, and dermaseptins, among others, have been investigated with promising in vitro results against various cancers. These compounds have even demonstrated efficacy against chemotherapy-resistant tumors. Additionally, they are synergistic with traditional chemotherapies because they act through separate mechanisms, which limits resistance resulting from selective tumor mutations. LL37 is currently being evaluated in Phase II clinical trials for melanoma, a traditionally immuno-responsive cancer, although results are not yet available. Another medication, derived from lactoferrin, LTX-315, has shown promise as a cancer therapeutic by disrupting plasma and mitochondrial membranes and recruiting effector T cells. It is being actively investigated in Phase I trials for use as monotherapy or in combination with other immunotherapies against transdermally accessible tumors, including melanoma, breast cancer, lymphoma, and head and neck cancers.
**Conclusions:**

HDPs have numerous properties that make them excellent candidates as therapies specifically suited for Plastic and Reconstructive Surgery applications. Promising pre-clinical data suggest an eventual role for HDPs as surgical dressings, wound healing adjuncts, antibiotics, and implant coatings, although clinical translation has not yet been successfully achieved for most compounds. As further research progresses, novel applications will be developed, and it can be expected that HDP-based therapies will become increasingly present in the practice of Plastic and Reconstructive Surgery. In particular, research focused on host defense peptides as wound care dressings is likely to revolutionize the care for acute and chronic wounds encountered by our specialty. Limitations observed with current compounds are likely to be overcome with molecular modifications, such as those discussed in the overview, to ensure the compounds are locally effective and resistant to degradation. Additionally, the development of wound care devices utilizing these compounds with strategic delivery systems may play a major role in the ultimate commercialization of HDP based products.
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