Title

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

Journal

Plastic & Reconstructive Surgery, 146(1)

ISSN

0032-1052

Authors

DeLong, Michael R
Tandon, Vickram J
Da Lio, Andrew L
et al.

Publication Date

2020-07-01

DOI

10.1097/prs.0000000000006910

Peer reviewed

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

Michael R. DeLong, M.D.,[1] Vickram J. Tandon, M.D.,[2] Andrew L. Da Lio, M.D.,[1] Timothy J. Deming, Ph.D.,[3] Paul S. Cederna, M.D.,[2]

1. Division of Plastic and Reconstructive Surgery, Department of Surgery, University of California Los Angeles; Los Angeles, California.
2. Section of Plastic Surgery, Department of Surgery, University of Michigan; Ann Arbor, Michigan.
3. Department of Bioengineering, University of California Los Angeles, Los Angeles, California.

This project has not been presented at any national or regional conference.

Short Running Head: Host Defense Peptides

Corresponding author:
Paul Cederna, M.D.
Chief, Section of Plastic Surgery
Robert Oneal Professor of Plastic Surgery
Professor, Department of Biomedical Engineering
2130 Taubman Center, 1500 E. Medical Center Dr.
Ann Arbor, MI 48109-0340
Telephone: (734) 998-6022
Fax: (734) 763-5354

Financial Disclosure Statement: The authors report no financial conflicts of interest. This study was not funded.

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 α-, β-, and θ- 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.[17,18] 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.[19,20]

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.[21–23] These peptides often have a linear structure, although some may adopt an extended poly-proline helix (Figure 4).[24] 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.[20]

The third structural group adopts a β-sheet secondary structure with or without disulfide links between sulfur-containing cysteine residues (Figure 4).[25] 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.[26] 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 phosphoylation, 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).[20] 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.[31,32] In contrast, eukaryotic cells typically have neutrally charged membrane components including phosphatidylethanolamine, phosphatidylcholine, and sphingomyelin.[33,34] 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.[35,36]

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.[40,41] 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).[42,43]

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.[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.[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.[48] Other HDPs completely cross the target membrane without any disruption and exert entirely intracellular mechanisms of action.[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.[50–54]

Immuno-modulation

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 *in vivo*. LL37 demonstrates significantly reduced bacteriocidal effects in physiologic concentrations of magnesium, calcium, and sodium.[57] Additionally, many HDPs display limited bacterial lysis in the presence of host cells, suggesting questionable *in vivo* efficacy.[58] These peptides are also often expressed in host tissues at concentrations below the minimal threshold for bacteriocidal activity.[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).[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.[61,62] These properties are distinct from the direct antimicrobial properties, and can be modified separately with different amino acid substitutions.[63] Synthetic analogs have also now been constructed without any *in vitro* activity against microbes but still retain protective properties *in vivo* based purely on the immuno-modulatory properties. These innate defense-regulator peptides (IDR-1) show *in vivo* efficacy against several multi-drug resistant organisms including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus*, and *Salmonella enterica*

[6,64,65] through selective immuno-stimulation of neutrophils and monocytes while simultaneously limiting deleterious inflammatory consequences.[66]

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.[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.[68,69] Additionally, HDPs appear to help regulate angiogenesis and help stimulate vascular growth in healing tissues.[70] These wound healing properties have been found to extend to multiple tissue types including intestinal and pulmonary epithelial wounds.[71–74]

Resistance

Bacterial resistance to HDPs is also an unfortunate reality that is clinically and experimentally observed.[75] In fact, infectious virulence has been correlated with resistance to HDPs for many bacterial organisms.[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.[79] 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.[80]

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.[81,82] 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.[83] Omiganan has also demonstrated excellent potential for acne and rosacea in pre-clinical pig skin colonization models.[84] 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.[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.[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.[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.[90,91] P10 is another fragment of LL37 which has proven to be effective against mupirocin-resistant MRSA strains and can neutrolize 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.[92] It additionally failed to improve mortality rates and ventilator-associated pneumonia in critically ill intubated patients

treated six times per day.[93] 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.[94] 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.[95] 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.[96,97] The application of hydrogels impregnated with an HDP in a rat burn model resulted in accelerated healing with reduced infection, inflammation, and oxidative stress.[98] 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.[99]

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.[100,101] Promising results were obtained using coatings based on melittin-cecropin peptides, which can be applied to a variety of surfaces and maintains is antimicrobial activity while minimizing host toxicity.[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.[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.[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.[107] With systemic

administration, these compounds can also inhibit the sepsis response with resulting improvements in the mortality rates of critically ill patients.[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.[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 (Bagsværd, Denmark), with promising preclinical data against multi-drug resistant bacteria.[109–111] While commercial development was halted, preclinical studies are actively ongoing with promising results.[112–116] Oragenics (Tampa, FL, USA) has investigated Mutacin 1140, a lantibiotic produced by *streptococcus mutans*, as a therapy for *clostridium difficile*.[88] They recently published efficacy of Mutacin 1140 in a hampster 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 *clostridium difficile*, and the drug is likely to be discontinued.[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 *meningococcemia* but failed phase III clinical trials.[118]

Therapeutics derived from HDPs have also been investigated for use against nonbacterial infectious pathogens.[119] Several peptides have direct anti-viral effects against strains of influenza.[120,121] 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.[122,123] Retrocyclin analogs can even protect host cells against traditionally antiviral-resistant HIV strains.[124] 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.[124]

Wound Healing

LL37 has also been evaluated as a topical wound healing therapy, specifically for venous stasis ulcers.[125] 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.[126] 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.[127] 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.[128] Phyloseptins, magainins, and dermaseptins, among others, have been investigated with promising *in vitro* results against various cancers.[129–132] These compounds have even demonstrated efficacy against chemotherapy-resistant tumors.[133] Additionally, they are synergistic with traditional chemotherapies because they act through separate mechanisms, which limits resistance resulting from selective tumor mutations.[134] LL37 is currently being evaluated in Phase II clinical trials for melanoma, a traditionally immuno-responsive cancer, although results are not yet available.[135] Another medication, derived from lactoferrin, LTX-315, has shown promise as a cancer therapeutic by disrupting plasma and mitochonrial membranes and recruiting effector T cells.[136] 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.[136]

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.

References:

1. Skarnes, Robert C., and Dennis W. Watson. “Antimicrobial factors of normal tissues and fluids.” *Bacteriol Rev*. 21.4 (1957.

2. Antimicrobial Peptide Database. *http://aps.unmc.edu/AP/main.php*. Accessed F.

3. Hancock REW, Lehrer R. Cationic peptides: A new source of antibiotics. *Trends Biotechnol*. 1998;16(2):82-88. doi:10.1016/S0167-7799(97)01156-6

4. Varnava KG, Ronimus RS, Sarojini V. A review on comparative mechanistic studies of antimicrobial peptides against archaea. *Biotechnol Bioeng*. 2017;114(11):2457-2473. doi:10.1002/bit.26387

5. Maróti Gergely G, Kereszt A, Kondorosi É, Mergaert P. Natural roles of antimicrobial peptides in microbes, plants and animals. *Res Microbiol*. 2011;162(4):363-374. doi:10.1016/j.resmic.2011.02.005

6. Scott MG, Dullaghan E, Mookherjee N, et al. An anti-infective peptide that selectively modulates the innate immune response. *Nat Biotechnol*. 2007;25(4):465-472. doi:10.1038/nbt1288

7. Frohm M, Agerberth B, Ahangari G, et al. The expression of the gene coding for the antibacterial peptide LL-37 is induced in human keratinocytes during inflammatory disorders. *J Biol Chem*. 1997;272(24):15258-15263. doi:10.1074/jbc.272.24.15258

8. Hancock RE, Patrzykat A. Clinical development of cationic antimicrobial peptides: from natural to novel antibiotics. *Curr Drug Targets Infect Disord*. 2002;2(1):79-83. doi:10.2174/1568005024605855

9. Zanetti M. The role of cathelicidins in the innate host defenses of mammals. *Curr Issues Mol Biol*. 2005;7(2):179-196.

10. Ramanathan B, Davis EG, Ross CR, Blecha F. Cathelicidins: Microbicidal activity, mechanisms of action, and roles in innate immunity. *Microbes Infect*. 2002;4(3):361-372. doi:10.1016/S1286-4579(02)01549-6

11. Zanetti M. Cathelicidins, multifunctional peptides of the innate immunity. *J Leukoc Biol*. 2003;75(1):39-48. doi:10.1189/jlb.0403147

12. Mangoni ML, Maisetta G, Di Luca M, et al. Comparative analysis of the bactericidal activities of amphibian peptide analogues against multidrug-resistant nosocomial bacterial strains. *Antimicrob Agents Chemother*. 2008;52(1):85-91. doi:10.1128/AAC.00796-07

13. Huang Y, Wiradharma N, Xu K, et al. Cationic amphiphilic alpha-helical

peptides for the treatment of carbapenem-resistant Acinetobacter baumannii infection. *Biomaterials*. 2012;33(34):8841-8847. doi:10.1016/j.biomaterials.2012.08.026

14. Laverty G, McLaughlin M, Shaw C, Gorman SP, Gilmore BF. Antimicrobial activity of short, synthetic cationic lipopeptides. *Chem Biol Drug Des*. 2010;75(6):563-569. doi:10.1111/j.1747-0285.2010.00973.x

15. Takahashi H, Caputo GA, Vemparala S, Kuroda K. Synthetic Random Copolymers as a Molecular Platform to Mimic Host-Defense Antimicrobial Peptides. *Bioconjug Chem*. 2017;28(5):1340-1350. doi:10.1021/acs.bioconjchem.7b00114

16. Strandberg E, Zerweck J, Horn D, et al. Influence of hydrophobic residues on the activity of the antimicrobial peptide magainin 2 and its synergy with PGLa. *J Pept Sci*. 2015;21(5):436-445. doi:10.1002/psc.2780

17. Johansson J, Gudmundsson GH, Rottenberg ME, Berndt KD, Agerberth B. Conformation-dependent antibacterial activity of the naturally occurring human peptide LL-37. *J Biol Chem*. 1998;273(6):3718-3724. doi:10.1074/jbc.273.6.3718

18. Avitabile C, D'Andrea LD, Romanelli A. Circular Dichroism studies on the interactions of antimicrobial peptides with bacterial cells. *Sci Rep*. 2014;4. doi:10.1038/srep04293

19. Omardien S, Brul S, Zaat SAJ. Antimicrobial Activity of Cationic Antimicrobial Peptides against Gram-Positives: Current Progress Made in Understanding the Mode of Action and the Response of Bacteria. *Front Cell Dev Biol*. 2016;4. doi:10.3389/fcell.2016.00111

20. Toke O. Antimicrobial peptides: New candidates in the fight against bacterial infections. *Biopolym - Pept Sci Sect*. 2005;80(6):717-735. doi:10.1002/bip.20286

21. Nguyen LT, Chau JK, Perry NA, de Boer L, Zaat SAJ, Vogel HJ. Serum stabilities of short tryptophan- and arginine-rich antimicrobial peptide analogs. *PLoS One*. 2010;5(9):1-8. doi:10.1371/journal.pone.0012684

22. Strøm MB, Rekdal O, Svendsen JS. Antimicrobial activity of short arginine- and tryptophan-rich peptides. *J Pept Sci*. 2002;8(8):431-437. doi:10.1002/psc.398

23. Chan DI, Prenner EJ, Vogel HJ. Tryptophan- and arginine-rich antimicrobial peptides: Structures and mechanisms of action. *Biochim Biophys Acta - Biomembr*. 2006;1758(9):1184-1202. doi:10.1016/j.bbamem.2006.04.006

24. Yount NY, Yeaman MR. Immunocontinuum: perspectives in antimicrobial peptide mechanisms of action and resistance. *Protein Pept Lett*. 2005;12(1):49-67. doi:10.2174/0929866053405959

25. Giuliani A, Pirri G, Nicoletto SF. Antimicrobial peptides: An overview of a promising class of therapeutics. *Cent Eur J Biol*. 2007;2(1):1-33. doi:10.2478/s11535-007-0010-5

26. Jenssen H, Hamill P, Hancock REW. Peptide antimicrobial agents. *Clin Microbiol Rev*. 2006;19(3):491-511. doi:10.1128/CMR.00056-05

27. Wilson SS, Wiens ME, Smith JG. Antiviral mechanisms of human defensins. *J Mol Biol*. 2013;425(24):4965-4980. doi:10.1016/j.jmb.2013.09.038

28. Kim HS, Yoon H, Minn I, et al. Pepsin-Mediated Processing of the Cytoplasmic Histone H2A to Strong Antimicrobial Peptide Buforin I. *J Immunol*. 2000;165(6):3268-3274. doi:10.4049/jimmunol.165.6.3268

29. Wang G. Post-Translational Modifications of Natural Antimicrobial Peptides and Strategies for Peptide Engineering. *Curr Biotechnol*. 2011;1(1):72-79. doi:10.2174/2211551X11201010072

30. Welling MM, Paulusma-Annema a, Balter HS, Pauwels EK, Nibbering PH. Technetium-99m labeled antimicrobial peptides discriminate between bacterial infections and sterile inflammations. *Eur J Nucl Med*. 2000;27(3):292-301. doi:10.1007/s002590000378

31. Scott MG, Gold MR, Hancock REW. Interaction of cationic peptides with lipoteichoic acid and gram- positive bacteria. *Infect Immun*. 1999;67(12):6445-6453.

32. Silvestro L, Gupta K, Weiser JN, Axelsen PH. The concentration-dependent membrane activity of cecropin A. *Biochemistry*. 1997;36(38):11452-11460. doi:10.1021/bi9630826

33. Nguyen LT, Haney EF, Vogel HJ. The expanding scope of antimicrobial peptide structures and their modes of action. *Trends Biotechnol*. 2011;29(9):464-472. doi:10.1016/j.tibtech.2011.05.001

34. Yeaman MR. Mechanisms of Antimicrobial Peptide Action and Resistance. *Pharmacol Rev*. 2003;55(1):27-55. doi:10.1124/pr.55.1.2

35. Dennison SR, Whittaker M, Harris F, Phoenix D a. Anticancer alpha-helical peptides and structure/function relationships underpinning their interactions with tumour cell membranes. *Curr Protein Pept Sci*. 2006;7:487-499. doi:10.2174/138920306779025611

36. Schröder-Borm H, Bakalova R, Andrä J. The NK-lysin derived peptide NK-

2 preferentially kills cancer cells with increased surface levels of negatively charged phosphatidylserine. *FEBS Lett*. 2005;579(27):6128-6134. doi:10.1016/j.febslet.2005.09.084

37. Pardo J, Perez-Galan P, Gamen S, et al. A Role of the Mitochondrial Apoptosis-Inducing Factor in Granulysin-Induced Apoptosis. *J Immunol*. 2001;167(3):1222-1229. doi:10.4049/jimmunol.167.3.1222

38. Kagan BL, Selsted ME, Ganz T, Lehrer RI. Antimicrobial defensin peptides form voltage-dependent ion-permeable channels in planar lipid bilayer membranes. *Proc Natl Acad Sci U S A*. 1990;87(January):210–214. doi:10.1073/pnas.87.1.210

39. Christensen B, Fink J, Merrifield RB, Mauzerall D. Channel-forming properties of cecropins and related model compounds incorporated into planar lipid membranes. *Proc Natl Acad Sci U S A*. 1988;85(14):5072-5076. doi:10.1073/pnas.85.14.5072

40. Matsuzaki K, Shioyama T, Okamura E, et al. A comparative study on interactions of a-aminoisobutyric acid containing antibiotic peptides, trichopolyn I and hypelcin A with phosphatidylcholine bilayers. *Biochim Biophys Acta*. 1991;1070(2):419-428. http://www.ncbi.nlm.nih.gov/pubmed/1764454.

41. Ben-Efraim I, Shai Y. The structure and organization of synthetic putative membranous segments of ROMK1 channel in phospholipid membranes. *Biophys J*. 1997;72(1):85-96. doi:10.1016/S0006-3495(97)78649-1

42. Turner J, Cho Y, Dinh NN, Waring AJ, Lehrer RI. Activities of LL-37, a cathelin-associated antimicrobial peptide of human neutrophils. *Antimicrob Agents Chemother*. 1998;42(9):2206-2214. doi:10.5021/ad.2012.24.2.126

43. Breukink E, De Kruijff B. The lantibiotic nisin, a special case or not? *Biochim Biophys Acta - Biomembr*. 1999;1462(1-2):223-234. doi:10.1016/S0005-2736(99)00208-4

44. Oren Z, Shai Y. Mode of action of linear amphipathic alpha-helical antimicrobial peptides. *Biopolymers*. 1998;47(6):451-463. doi:10.1002/(SICI)1097-0282(1998)47:6<451::AID-BIP4>3.0.CO;2-F

45. Bechinger B. The structure, dynamics and orientation of antimicrobial peptides in membranes by multidimensional solid-state NMR spectroscopy. *Biochim Biophys Acta - Biomembr*. 1999;1462(1-2):157-183. doi:10.1016/S0005-2736(99)00205-9

46. Matsuzaki K, Murase O, Fujii N, Miyajima K. An antimicrobial peptide, magainin 2, induced rapid flip-flop of phospholipids coupled with pore

formation and peptide translocation. *Biochemistry*. 1996;35(35):11361-11368. doi:10.1021/bi960016v

47. Ludtke SJ, He K, Heller WT, Harroun TA, Yang L, Huang HW. Membrane pores induced by magainin. *Biochemistry*. 1996;35(43):13723-13728. doi:10.1021/bi9620621

48. Wenzel M, Chiriac AI, Otto A, et al. Small cationic antimicrobial peptides delocalize peripheral membrane proteins. *Proc Natl Acad Sci U S A*. 2014;111(14):E1409-18. doi:10.1073/pnas.1319900111

49. Park CB, Yi K-S, Matsuzaki K, Kim MS, Kim SC. Structure-activity analysis of buforin II, a histone H2A-derived antimicrobial peptide: The proline hinge is responsible for the cell-penetrating ability of buforin II. *Proc Natl Acad Sci*. 2000;97(15):8245-8250. doi:10.1073/pnas.150518097

50. Mathew B, Nagaraj R. Antimicrobial activity of human α-defensin 6 analogs: Insights into the physico-chemical reasons behind weak bactericidal activity of HD6 in vitro. *J Pept Sci*. 2015;21(11):811-818. doi:10.1002/psc.2821

51. Ghosh A, Kar RK, Jana J, et al. Indolicidin targets duplex DNA: Structural and mechanistic insight through a combination of spectroscopy and microscopy. *ChemMedChem*. 2014;9(9):2052-2058. doi:10.1002/cmdc.201402215

52. Xiong Y-Q, Bayer AS, Yeaman MR. Inhibition of intracellular macromolecular synthesis in Staphylococcus aureus by thrombin-induced platelet microbicidal proteins. *J Infect Dis*. 2002;185:348-356. doi:10.1086/338514

53. Leeuw E de, Li C, Zeng P, et al. Functional interaction of human neutrophil peptide-1 with the cell wall precursor lipid II. *FEBS Lett*. 2010;584(8):1543-1548. doi:10.1016/j.febslet.2010.03.004

54. Otvos L. Antibacterial peptides and proteins with multiple cellular targets. *J Pept Sci*. 2005;11(11):697-706. doi:10.1002/psc.698

55. Kraemer BF, Campbell RA, Schwertz H, et al. Novel anti-bacterial activities of β-defensin 1 in human platelets: Suppression of pathogen growth and signaling of neutrophil extracellular trap formation. *PLoS Pathog*. 2011;7(11). doi:10.1371/journal.ppat.1002355

56. Wilmes M, Stockem M, Bierbaum G, et al. Killing of Staphylococci by θ-Defensins Involves Membrane Impairment and Activation of Autolytic Enzymes. *Antibiotics*. 2014;3(4):617-631. doi:10.3390/antibiotics3040617

57. Bowdish DME. Impact of LL-37 on anti-infective immunity. *J Leukoc Biol*.

2004;77(4):451-459. doi:10.1189/jlb.0704380

58. Starr CG, He J, Wimley WC. Host Cell Interactions Are a Significant Barrier to the Clinical Utility of Peptide Antibiotics. *ACS Chem Biol*. 2016;11(12):3391-3399. doi:10.1021/acschembio.6b00843

59. Scott MG, Davidson DJ, Gold MR, Bowdish D, Hancock REW. The Human Antimicrobial Peptide LL-37 Is a Multifunctional Modulator of Innate Immune Responses. *J Immunol*. 2002;169(7):3883-3891. doi:10.4049/jimmunol.169.7.3883

60. Ruan Y, Shen T, Wang Y, Hou M, Li J, Sun T. Antimicrobial peptide LL-37 attenuates LTA induced inflammatory effect in macrophages. *Int Immunopharmacol*. 2013;15(3):575-580. doi:10.1016/j.intimp.2013.01.012

61. Cirioni O, Giacometti A, Ghiselli R, et al. LL-37 protects rats against lethal sepsis caused by gram-negative bacteria. *Antimicrob Agents Chemother*. 2006;50(5):1672-1679. doi:10.1128/AAC.50.5.1672-1679.2006

62. Hirata M, Shimomura Y, Yoshida M, Wright SC, Larrick JW. Endotoxin-binding synthetic peptides with endotoxin-neutralizing, antibacterial and anticoagulant activities. *Prog Clin Biol Res*. 1994;388:147-159.

63. Nan YH, Bang JK, Jacob B, Park IS, Shin SY. Prokaryotic selectivity and LPS-neutralizing activity of short antimicrobial peptides designed from the human antimicrobial peptide LL-37. *Peptides*. 2012;35(2):239-247. doi:10.1016/j.peptides.2012.04.004

64. Nijnik A, Madera L, Ma S, et al. Synthetic Cationic Peptide IDR-1002 Provides Protection against Bacterial Infections through Chemokine Induction and Enhanced Leukocyte Recruitment. *J Immunol*. 2010;184(5):2539-2550. doi:10.4049/jimmunol.0901813

65. Hou M, Zhang N, Yang J, et al. Antimicrobial peptide LL-37 and IDR-1 ameliorate MRSA pneumonia in vivo. *Cell Physiol Biochem*. 2013;32(3):614-623. doi:10.1159/000354465

66. North JR, Takenaka S, Rozek A, et al. A novel approach for emerging and antibiotic resistant infections: Innate defense regulators as an agnostic therapy. *J Biotechnol*. 2016;226:24-34. doi:10.1016/j.jbiotec.2016.03.032

67. Mangoni ML, Mcdermott AM, Zasloff M. Antimicrobial peptides and wound healing: Biological and therapeutic considerations. *Exp Dermatol*. 2016;25(3):167-173. doi:10.1111/exd.12929

68. Hirsch T, Spielmann M, Zuhaili B, et al. Human beta-defensin-3

promotes wound healing in infected diabetic wounds. *J Gene Med*. 2009;11(3):220-228. doi:10.1002/jgm.1287

69. Niyonsaba F, Ushio H, Hara M, et al. Antimicrobial Peptides Human -Defensins and Cathelicidin LL-37 Induce the Secretion of a Pruritogenic Cytokine IL-31 by Human Mast Cells. *J Immunol*. 2010;184(7):3526-3534. doi:10.4049/jimmunol.0900712

70. Koczulla R, Von Degenfeld G, Kupatt C, et al. An angiogenic role for the human peptide antibiotic LL-37/hCAP-18. *J Clin Invest*. 2003;111(11):1665-1672. doi:10.1172/JCI17545

71. Shaykhiev R. Human endogenous antibiotic LL-37 stimulates airway epithelial cell proliferation and wound closure. *AJP Lung Cell Mol Physiol*. 2005;289(5):L842-L848. doi:10.1152/ajplung.00286.2004

72. Sheng Q, Lv Z, Cai W, et al. Human beta-defensin-3 promotes intestinal epithelial cell migration and reduces the development of necrotizing enterocolitis in a neonatal rat model. *Pediatr Res*. 2014;76(3):269-279. doi:10.1038/pr.2014.93

73. Otte JM, Werner I, Brand S, et al. Human beta defensin 2 promotes intestinal wound healing in vitro. *J Cell Biochem*. 2008;104(6):2286-2297. doi:10.1002/jcb.21787

74. Di Meglio P, Perera GK, Nestle FO. The Multitasking Organ: Recent Insights into Skin Immune Function. *Immunity*. 2011;35(6):857-869. doi:10.1016/j.immuni.2011.12.003

75. Peschel A, Sahl HG. The co-evolution of host cationic antimicrobial peptides and microbial resistance. *Nat Rev Microbiol*. 2006;4(7):529-536. doi:10.1038/nrmicro1441

76. Kraus D, Peschel a. Molecular mechanisms of bacterial resistance to antimicrobial peptides. *Curr Top Microbiol Immunol*. 2006;306:231-250.

77. Van 'T Hof W, Veerman ECI, Heimerhorst EJ, Nieuw Amerongen A V. Antimicrobial peptides: Properties and applicability. *Biol Chem*. 2001;382(4):597-619. doi:10.1515/BC.2001.072

78. Zasloff M. Magainins, a class of antimicrobial peptides from \ textit{Xenopus} skin: isolation, characterization of two active forms, and partial cDNA sequence of a precursor. *Proc Natl Acad Sci U S A*. 1987;84(15):5449-5453. doi:10.1097/00043764-198806000-00004

79. Lamb HM, Wiseman LR. Pexiganan acetate. *Drugs*. 1998;56(6):1047-1052. doi:10.2165/00003495-199856060-00011

80. Dipexium's Diabetic Foot Ulcer Candidate Fails Phase III Trials.

https://www.genengnews.com/gen-news-highlights/dipexiums-diabetic-foot-ulcer-candidate-fails-phase-iii-trials/81253359. Accessed 3.23.2018.

81. Sader HS, Fedler KA, Rennie RP, Stevens S, Jones RN. Omiganan pentahydrochloride (MBI 226), a topical 12-amino-acid cationic peptide: Spectrum of antimicrobial activity and measurements of bactericidal activity. *Antimicrob Agents Chemother*. 2004;48(8):3112-3118. doi:10.1128/AAC.48.8.3112-3118.2004

82. Fritsche TR, Rhomberg PR, Sader HS, Jones RN. Antimicrobial activity of omiganan pentahydrochloride tested against contemporary bacterial pathogens commonly responsible for catheter-associated infections. *J Antimicrob Chemother*. 2008;61(5):1092-1098. doi:10.1093/jac/dkn074

83. Study of Omiganan 1% Gel in Preventing Catheter Infections/Colonization in Patients With Central Venous Catheters. https://clinicaltrials.gov/ct2/show/results/NCT00231153. Accessed March 23, 2018.

84. Rubinchik E, Dugourd D, Algara T, Pasetka C, Friedland HD. Antimicrobial and antifungal activities of a novel cationic antimicrobial peptide, omiganan, in experimental skin colonisation models. *Int J Antimicrob Agents*. 2009;34(5):457-461. doi:10.1016/j.ijantimicag.2009.05.003

85. Bylund J, Christophe T, Boulay F, Nyström T, Karlsson A, Dahlgren C. Proinflammatory activity of a cecropin-like antibacterial peptide from Helicobacter pylori. *Antimicrob Agents Chemother*. 2001;45(6):1700-1704. doi:10.1128/AAC.45.6.1700-1704.2001

86. Park SC, Kim MH, Hossain MA, et al. Amphipathic α-helical peptide, HP (2-20), and its analogues derived from Helicobacter pylori: Pore formation mechanism in various lipid compositions. *Biochim Biophys Acta - Biomembr*. 2008;1778(1):229-241. doi:10.1016/j.bbamem.2007.09.020

87. Ryu S, Park Y, Kim B, et al. Inhibitory and anti-inflammatory effects of the Helicobacter pylori-derived antimicrobial peptide HPA3NT3 against Propionibacterium acnes in the skin. *Br J Dermatol*. 2014;171(6):1358-1367. doi:10.1111/bjd.13480

88. Smith L, Zachariah C, Thirumoorthy R, et al. Structure and dynamics of the lantibiotic mutacin 1140. *Biochemistry*. 2003;42(35):10372-10384. doi:10.1021/bi034490u

89. Malanovic N, Leber R, Schmuck M, et al. Phospholipid-driven differences determine the action of the synthetic antimicrobial peptide OP-145 on

Gram-positive bacterial and mammalian membrane model systems. *Biochim Biophys Acta - Biomembr*. 2015;1848(10):2437-2447. doi:10.1016/j.bbamem.2015.07.010

90. Haisma EM, De Breij A, Chan H, et al. LL-37-derived peptides eradicate multidrug-resistant Staphylococcus aureus from thermally wounded human skin equivalents. *Antimicrob Agents Chemother*. 2014;58(8):4411-4419. doi:10.1128/AAC.02554-14

91. Göblyös A, Schimmel KJM, Valentijn ARPM, et al. Development of a Nose Cream Containing the Synthetic Antimicrobial Peptide P60.4Ac for Eradication of Methicillin-Resistant Staphylococcus aureus Carriage. *J Pharm Sci*. 2013;102(10):3539-3544. doi:10.1002/jps.23695

92. Trotti A, Garden A, Warde P, et al. A multinational, randomized phase iii trial of iseganan hcl oral solution for reducing the severity of oral mucositis in patients receiving radiotherapy for head-and-neck malignancy. *Int J Radiat Oncol Biol Phys*. 2004;58(3):674-681. doi:10.1016/S0360-3016(03)01627-4

93. Kollef M, Pittet D, García MS, et al. A randomized double-blind trial of iseganan in prevention of ventilator-associated pneumonia. *Am J Respir Crit Care Med*. 2006;173(1):91-97. doi:10.1164/rccm.200504-656OC

94. Elad S, Epstein JB, Raber-Durlacher J, Donnelly P, Strahilevitz J. The antimicrobial effect of Iseganan HCl oral solution in patients receiving stomatotoxic chemotherapy: analysis from a multicenter, double-blind, placebo-controlled, randomized, phase III clinical trial. *J Oral Pathol Med*. 2012;41(3):229-234. doi:Doi 10.1111/J.1600-0714.2011.01094.X

95. Yu HY, Tu CH, Yip BS, et al. Easy strategy to increase salt resistance of antimicrobial peptides. *Antimicrob Agents Chemother*. 2011;55(10):4918-4921. doi:10.1128/AAC.00202-11

96. Milner SM, Ortega MR. Reduced antimicrobial peptide expression in human burn wounds. *Burns*. 1999;25:411-413. doi:10.1016/S0305-4179(98)00192-2

97. Bhat S, Milner S. Antimicrobial peptides in burns and wounds. *Curr Protein Pept Sci*. 2007;8(5):506-520. doi:10.2174/138920307782411428

98. Silva JP, Dhall S, Garcia M, et al. Improved burn wound healing by the antimicrobial peptide LLKKK18 released from conjugates with dextrin embedded in a carbopol gel. *Acta Biomater*. 2015;26:249-262. doi:10.1016/j.actbio.2015.07.043

99. Huang H-N, Pan C-Y, Wu H-Y, Chen J-Y. Antimicrobial peptide Epinecidin-1 promotes complete skin regeneration of methicillin-resistant

<i>Staphylococcus aureus</i>-infected burn wounds in a swine model. *Oncotarget*. 2017. doi:10.18632/oncotarget.15042

100. Bevilacqua MP, Huang DJ, Wall BD, et al. Amino Acid Block Copolymers with Broad Antimicrobial Activity and Barrier Properties. *Macromol Biosci*. 2017;17(10). doi:10.1002/mabi.201600492

101. De La Fuente-Núñez C, Korolik V, Bains M, et al. Inhibition of bacterial biofilm formation and swarming motility by a small synthetic cationic peptide. *Antimicrob Agents Chemother*. 2012;56(5):2696-2704. doi:10.1128/AAC.00064-12

102. Rai A, Pinto S, Evangelista MB, et al. High-density antimicrobial peptide coating with broad activity and low cytotoxicity against human cells. *Acta Biomater*. 2016;33:64-74. doi:10.1016/j.actbio.2016.01.035

103. Gao Q, Yu M, Su Y, et al. Rationally designed dual functional block copolymers for bottlebrush-like coatings: In vitro and in vivo antimicrobial, antibiofilm, and antifouling properties. *Acta Biomater*. 2017;51:112-124. doi:10.1016/j.actbio.2017.01.061

104. Riool M, de Breij A, Drijfhout JW, Nibbering PH, Zaat SAJ. Antimicrobial Peptides in Biomedical Device Manufacturing. *Front Chem*. 2017. doi:10.3389/fchem.2017.00063

105. Güzel Y, Elmadag M, Uzer G, Yıldız F, Bilsel K, Tuncay İ. Cytotoxicity of a new antimicrobial coating for surgical screws: An in vivo study. *Singapore Med J*. 2017;58(1):46-49. doi:10.11622/smedj.2016021

106. Hickok NJ, Shapiro IM. Immobilized antibiotics to prevent orthopaedic implant infections. *Adv Drug Deliv Rev*. 2012;64(12):1165-1176. doi:10.1016/j.addr.2012.03.015

107. Srinivas N, Jetter P, Ueberbacher BJ, et al. Peptidomimetic antibiotics target outer-membrane biogenesis in pseudomonas aeruginosa. *Science (80-)*. 2010;327(5968):1010-1013. doi:10.1126/science.1182749

108. Maiti S, Patro S, Purohit S, Jain S, Senapati S, Dey N. Effective control of salmonella infections by employing combinations of recombinant antimicrobial human β-Defensins hBD-1 and hBD-2. *Antimicrob Agents Chemother*. 2014;58(11):6896-6903. doi:10.1128/AAC.03628-14

109. Xiong YQ, Hady WA, Deslandes A, et al. Efficacy of NZ2114, a novel plectasin-derived cationic antimicrobial peptide antibiotic, in experimental endocarditis due to methicillin-resistant Staphylococcus aureus. *Antimicrob Agents Chemother*. 2011;55(11):5325-5330. doi:10.1128/AAC.00453-11

110. Mygind PH, Fischer RL, Schnorr KM, et al. Plectasin is a peptide antibiotic with therapeutic potential from a saprophytic fungus. *Nature*. 2005;437(7061):975-980. doi:10.1038/nature04051

111. Andes D, Craig W, Nielsen LA, Kristensen HH. In vivo pharmacodynamic characterization of a novel plectasin antibiotic, NZ2114, in a murine infection model. *Antimicrob Agents Chemother*. 2009;53(7):3003-3009. doi:10.1128/AAC.01584-08

112. Li L, Wang L, Gao Y, Wang J, Zhao X. Effective antimicrobial activity of plectasin-derived antimicrobial peptides against Staphylococcus aureus infection in mammary glands. *Front Microbiol*. 2017;8(DEC). doi:10.3389/fmicb.2017.02386

113. Mao R, Teng D, Wang X, et al. Optimization of expression conditions for a novel NZ2114-derived antimicrobial peptide-MP1102 under the control of the GAP promoter in Pichia pastoris X-33 Applied microbiology. *BMC Microbiol*. 2015;15(1). doi:10.1186/s12866-015-0389-5

114. Klein K, Grønnemose RB, Alm M, Brinch KS, Kolmos HJ, Andersen TE. Controlled release of plectasin NZ2114 from a hybrid silicone-hydrogel material for inhibition of Staphylococcus aureus biofilm. *Antimicrob Agents Chemother*. 2017;61(7). doi:10.1128/AAC.00604-17

115. Chen H, Mao R, Teng D, et al. Design and pharmacodynamics of recombinant NZ2114 histidine mutants with improved activity against methicillin-resistant Staphylococcus aureus. *AMB Express*. 2017;7(1). doi:10.1186/s13568-017-0345-x

116. Fox JL. Antimicrobial peptides stage a comeback. *Nat Biotechnol*. 2013;31(5):379-382. doi:10.1038/nbt.2572

117. Pachón-Ibáñez ME, Smani Y, Pachón J, Sánchez-Céspedes J. Perspectives for clinical use of engineered human host defense antimicrobial peptides. *FEMS Microbiol Rev*. 2017;41(3):323-342. doi:10.1093/femsre/fux012

118. Gordon YJ, Romanowski EG, McDermott AM. A Review of Antimicrobial Peptides and Their Therapeutic Potential as Anti-Infective Drugs. *Curr Eye Res*. 2005. doi:10.1080/02713680590968637

119. Wang G. Natural antimicrobial peptides as promising anti-HIV candidates. *Curr Top Pept Protein Res*. 2012;13:93-110.

120. Doss M, Ruchala P, Tecle T, et al. Hapivirins and Diprovirins: Novel -Defensin Analogs with Potent Activity against Influenza A Virus. *J Immunol*. 2012;188(6):2759-2768. doi:10.4049/jimmunol.1101335

121. Tripathi S, Tecle T, Verma A, Crouch E, White M, Hartshorn KL. The human cathelicidin LL-37 inhibits influenza a viruses through a mechanism distinct from that of surfactant protein d or defensins. *J Gen Virol*. 2013;94(PART11):40-49. doi:10.1099/vir.0.045013-0

122. Cole AM, Hong T, Boo LM, et al. Retrocyclin: a primate peptide that protects cells from infection by T- and M-tropic strains of HIV-1. *Proc Natl Acad Sci U S A*. 2002;99(4):1813-1818. doi:10.1073/pnas.052706399

123. Münk C, Wei G, Yang OO, et al. The theta-defensin, retrocyclin, inhibits HIV-1 entry. *AIDS Res Hum Retroviruses*. 2003;19(10):875-881. doi:10.1089/088922203322493049

124. Wood MP, Cole AL, Ruchala P, et al. A Compensatory Mutation Provides Resistance to Disparate HIV Fusion Inhibitor Peptides and Enhances Membrane Fusion. *PLoS One*. 2013;8(2). doi:10.1371/journal.pone.0055478

125. Grönberg A, Mahlapuu M, Ståhle M, Whately-Smith C, Rollman O. Treatment with LL-37 is safe and effective in enhancing healing of hard-to-heal venous leg ulcers: a randomized, placebo-controlled clinical trial. *Wound Repair Regen*. 2014;22(5):613-621. doi:10.1111/wrr.12211

126. Krejner A, Litwiniuk M, Grzela T. LL-37 but Not 25-Hydroxy-Vitamin D Serum Level Correlates with Healing of Venous Leg Ulcers. *Arch Immunol Ther Exp (Warsz)*. 2017. doi:10.1007/s00005-016-0423-9

127. Nakagami H, Sugimoto K, Ishikawa T, et al. Physician-initiated clinical study of limb ulcers treated with a functional peptide, SR-0379: from discovery to a randomized, double-blind, placebo-controlled trial. *npj Aging Mech Dis*. 2018. doi:10.1038/s41514-018-0021-7

128. Deslouches B, Peter Di Y. Antimicrobial peptides with selective antitumor mechanisms: prospect for anticancer applications. *Oncotarget*. 2017. doi:10.18632/oncotarget.16743

129. Baker MA, Maloy WL, Zasloff M, Jacob LS. Anticancer Efficacy of Magainin2 and Analogue Peptides. *Cancer Res*. 1993;53(13):3052-3057.

130. Wan Y, Ma C, Zhou M, et al. Phylloseptin-PBa—a novel broad-spectrum antimicrobial peptide from the skin secretion of the Peruvian purple-sided leaf frog (Phyllomedusa baltea) which exhibits cancer cell cytotoxicity. *Toxins (Basel)*. 2015;7(12):5182-5193. doi:10.3390/toxins7124878

131. Liu J, Wu Q, Li L, et al. Discovery of phylloseptins that defense against gram-positive bacteria and inhibit the proliferation of the non-small cell lung cancer cell line, from the skin secretions of phyllomedusa frogs.

Molecules. 2017;22(9). doi:10.3390/molecules22091428

132. Huang L, Chen D, Wang L, et al. Dermaseptin-PH: A novel peptide with antimicrobial and anticancer activities from the skin secretion of the south American orange-legged leaf frog, pithecopus (phyllomedusa) hypochondrialis. *Molecules*. 2017;22(10). doi:10.3390/molecules22101805

133. Johnstone SA, Gelmon K, Mayer LD, Hancock RE, Bally MB. In vitro characterization of the anticancer activity of membrane-active cationic peptides. I. Peptide-mediated cytotoxicity and peptide-enhanced cytotoxic activity of doxorubicin against wild-type and p-glycoprotein over-expressing tumor cell lines. *Anticancer Drug Des*. 2000;15(2):151-160. http://www.ncbi.nlm.nih.gov/pubmed/10901303.

134. Leuschner C, Hansel W. Membrane disrupting lytic peptides for cancer treatments. *Curr Pharm Des*. 2004;10(19):2299-2310. doi:10.2174/1381612043383971

135. Intratumoral Injections of LL37 for Melanoma. https://clinicaltrials.gov/ct2/show/NCT02225366. Accessed March 24, 2018.

136. Sveinbjørnsson B, Camilio KA, Haug BE, Rekdal Ø. LTX-315: a first-in-class oncolytic peptide that reprograms the tumor microenvironment. *Future Med Chem*. 2017;9(12):1339-1344. doi:10.4155/fmc-2017-0088