

RESEARCH MONOGRAPH . COMPOUND PROFILE

LL-37

The sole human cathelicidin-derived antimicrobial peptide, a 37-residue amphipathic alpha-helical cationic peptide released from the precursor protein hCAP-18 by proteinase 3 cleavage, possessing direct broad-spectrum antimicrobial activity through membrane disruption and pleiotropic immunomodulatory functions mediated by formyl peptide receptor 2, P2X7, and toll-like receptor signaling.

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ABSTRACT

LL-37, the carboxy-terminal 37-residue peptide of human cationic antimicrobial protein 18 (hCAP-18), is the only cathelicidin-derived antimicrobial peptide identified in the human genome and is a central effector of innate immune defense across epithelial surfaces, wound repair, and inflammatory regulation. The peptide was first identified as FALL-39 by Gudmundsson, Agerberth, and colleagues at the Karolinska Institutet in 1996 through screening of a human bone marrow cDNA library [1], and the mature processed form was subsequently designated LL-37 on the basis of its amino-terminal leucine-leucine sequence and 37-residue length [2]. hCAP-18, the 18-kilodalton holoprotein precursor, is constitutively stored in the specific granules of neutrophils and is released and proteolytically processed by neutrophil-derived proteinase 3 at sites of infection and inflammation to yield the biologically active LL-37 fragment [3]. The peptide adopts an amphipathic alpha-helical conformation in membrane-mimetic environments and exerts direct antimicrobial activity against gram-positive and gram-negative bacteria, enveloped viruses, and fungi through electrostatic interaction with anionic microbial membranes followed by membrane permeabilization and disruption [4, 5]. Beyond direct microbicidal activity, LL-37 functions as a multifunctional immunomodulatory mediator: it signals through formyl peptide receptor 2 (FPR2/ALX) to recruit neutrophils, monocytes, and T cells [6]; it neutralizes bacterial lipopolysaccharide and prevents endotoxin-driven inflammatory cascades [7]; it promotes angiogenesis and wound re-epithelialization through epidermal growth factor receptor transactivation [8]; and it modulates adaptive immune responses

through effects on dendritic cell maturation and T helper cell polarization [9]. Expression of hCAP-18/LL-37 is transcriptionally regulated by 1,25-dihydroxyvitamin D₃ through a vitamin D response element in the CAMP gene promoter, a mechanism first characterized by Liu et al. (2006) in a landmark demonstration that toll-like receptor activation of human macrophages by *Mycobacterium tuberculosis* triggers CYP27B1-mediated conversion of 25-hydroxyvitamin D to the active 1,25-dihydroxy form, which then induces cathelicidin expression and intracellular killing of the mycobacterium [10]. This vitamin D-cathelicidin axis has become a major research focus in tuberculosis, respiratory infection, and immunodeficiency. Clinical translation of LL-37 has advanced through Phase I and Phase II trials in chronic wound healing, where topical application of synthetic LL-37 at 0.5 and 1.6 mg/mL produced healing rate constants approximately three- to six-fold greater than placebo in hard-to-heal venous leg ulcers [11], and through a Phase IIb multicenter trial of 148 patients that identified a subgroup benefit in ulcers exceeding 10 cm² [12]. A randomized trial of recombinant LL-37 delivered via *Lactococcus lactis* as oral therapy against SARS-CoV-2 Omicron BA.5.1.3 demonstrated significant shortening of viral RNA negative conversion time with early intervention and acceptable safety [13]. The peptide is also implicated in the pathogenesis of rosacea, where aberrant processing of cathelicidin by kallikrein 5 serine protease generates proinflammatory LL-37 fragments in facial skin [14]; in psoriasis, where LL-37 complexed with self-DNA activates plasmacytoid dendritic cells through toll-like receptor 9 [15]; and in cancer biology, where context-dependent pro-tumorigenic and anti-tumorigenic effects have been reported across colorectal, breast, ovarian, and lung malignancies [16, 17]. Pharmacokinetically, the peptide is susceptible to rapid

proteolytic degradation in serum with a half-life of minutes to hours depending on protease milieu, limiting systemic bioavailability and driving research toward local and topical delivery, protease-resistant analogs, d-amino acid substitutions, and nanoparticle encapsulation strategies [18, 19]. The compound is commercially available as a synthetic peptide at greater than 95 percent purity from multiple peptide synthesis suppliers. This monograph reviews the chemistry, structure, and processing of LL-37; the molecular pharmacology including direct antimicrobial mechanisms and immunomodulatory receptor signaling; the vitamin D transcriptional axis; preclinical pharmacology across infection, inflammation, and wound healing models; the clinical evidence base in chronic wounds, infectious disease, and dermatologic conditions; reconstitution and handling; stack interactions; adverse events and safety signals including the rosacea and psoriasis pathogenic associations; and a comparative assessment of five alternative antimicrobial and immunomodulatory peptide candidates against LL-37 on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Designation: LL-37.

Systematic peptide name: The 37-residue carboxy-terminal cleavage product of human cationic antimicrobial protein 18 (hCAP-18), beginning with the dipeptide leucine-leucine (positions 134 to 170 of the full-length prepro-hCAP-18 sequence).

Precursor designations: hCAP-18 (human Cationic Antimicrobial Protein of 18 kDa); FALL-39 (the original designation based on the first four amino acids phenyl-alanine-alanine-leucine-leucine before the mature processing site was established) [1]; CAP-18 (generic cathelicidin antimicrobial protein 18).

Gene name: CAMP (cathelicidin antimicrobial peptide); chromosome 3p21.31 in the human genome. The gene encodes the full-length prepro-hCAP-18 protein of 170 amino acid residues, comprising a signal peptide, a cathelin-like domain of approximately 100 residues, and the carboxy-terminal LL-37 domain [1, 2].

UniProt accession: P49913 (CAMP_HUMAN).

DrugBank accession: DB16076 (investigational).

Other synonyms in the literature: CRAMP (cathelicidin-related antimicrobial peptide) refers to the murine ortholog, not LL-37 itself; investigators should distinguish the human peptide (LL-37, 37 residues, LLGDFFRKSKEKIGKEFKRIVQRIKDFLRNLPRTES) from the murine peptide (CRAMP, 34 residues) in cross-species translational studies.

1.2 Structural class and chemistry

LL-37 is a linear cationic antimicrobial peptide of the cathelicidin family, the sole member of this family encoded in the human genome. The cathelicidin family is defined by the conserved cathelin-like propiece domain of the precursor protein; the mature carboxy-terminal peptides vary substantially in sequence and structure

across mammalian species but share the common feature of cationic charge at physiological pH and amphipathic character that enables membrane interaction [20].

Primary sequence: LLGDDFRKSKEKIGKEFKRIVQRIKDFLRNLVPRTES (37 amino acid residues; single-letter code). The sequence contains no disulfide bonds and no post-translational modifications in the mature secreted form.

Molecular formula: C₂₀₅H₃₄₀N₆₀O₅₃ (free acid form of the peptide).

Molecular weight: 4493.33 Da (average isotopic mass of the free acid form). The molecular weight varies by approximately 18 Da depending on carboxy-terminal amidation status; the native human peptide is the free acid form (carboxy-terminal glutamic acid followed by serine).

Net charge: +6 at pH 7.4. The cationic character is attributable to six lysine residues (positions 8, 10, 12, 15, 18, 25), three arginine residues (positions 7, 19, 23, 29, 34), offset by two aspartate (positions 4, 26) and two glutamate (positions 11, 16, 36) residues.

Isoelectric point: Approximately 10.6.

Secondary structure: In aqueous solution at neutral pH, LL-37 is predominantly unstructured or adopts a random coil conformation. Upon interaction with anionic lipid membranes, detergent micelles, or membrane-mimetic solvents (such as trifluoroethanol or sodium dodecyl sulfate micelles), the peptide folds into a continuous amphipathic alpha-helix spanning approximately residues 2 to 31, with a disordered carboxy-terminal tail from residues 32 to 37 [4, 21]. The alpha-helical conformation segregates cationic and hydrophobic residues to opposite faces of the helix, producing the amphipathic character required for membrane binding and disruption.

Physical properties: White to off-white lyophilized powder when supplied as a synthetic peptide. Freely soluble in water at concentrations up to approximately 5 mg/mL; soluble in dimethyl sulfoxide; soluble in dilute acetic acid. The peptide self-associates in solution at concentrations above approximately 4 micromolar, forming oligomeric assemblies that may influence biological activity and complicate dose-response interpretation in vitro [22].

1.3 Synthesis and processing

The native biosynthetic route for LL-37 proceeds through transcription and translation of the CAMP gene to produce the 170-residue prepro-hCAP-18 protein. The signal peptide is removed co-translationally, yielding the 153-residue pro-hCAP-18 holoprotein, which is stored in the specific (secondary) granules of neutrophils in its inactive proform. Upon neutrophil degranulation at sites of infection or tissue injury, hCAP-18 is released into the extracellular space and is processed by the serine protease proteinase 3 (also stored in azurophilic granules and released upon activation), which cleaves between alanine-133 and leucine-134 of the full-length sequence to release the mature LL-37 peptide [3]. In seminal plasma, the processing enzyme is gastricsin (pepsin C), which cleaves hCAP-18 at a slightly different site to produce ALL-38, a 38-residue peptide one residue longer than LL-37 at the amino terminus [23].

Synthetic LL-37 for research use is produced by solid-phase peptide synthesis (SPPS), predominantly using 9-fluorenylmethyloxycarbonyl (Fmoc) chemistry on polystyrene or polyethylene glycol-polystyrene resin. The 37-residue length is within the practical range of modern automated SPPS, though the hydrophobic segment in the mid-sequence (residues 17 to 26) can produce aggregation on resin and reduce coupling efficiency. Standard synthesis employs double coupling at difficult residues and piperidine deprotection cycles. The crude peptide is purified by reversed-phase high-performance liquid chromatography (RP-HPLC) on C18 columns with acetonitrile-water-trifluoroacetic acid gradients and characterized by electrospray ionization mass spectrometry and analytical HPLC. Commercial synthetic LL-37 is available at greater than 95 percent purity (by HPLC area percent) from multiple peptide suppliers (AnaSpec, Bachem, GenScript, Tocris, Sigma-Aldrich, Phoenix Pharmaceuticals, InvivoGen, and others) at prices of approximately \$200 to \$600 per milligram at the time of monograph preparation.

Recombinant production of LL-37 has been demonstrated in *Escherichia coli*, *Pichia pastoris*, and *Lactococcus lactis* expression systems, typically as fusion proteins with cleavable tags (SUMO, intein, thioredoxin) to prevent toxicity to the host cell [13, 24]. The *Lactococcus lactis* system has been advanced to clinical trial as a delivery vehicle for oral LL-37 in the treatment of SARS-CoV-2 infection [13].

2. Abstract

LL-37, the sole cathelicidin antimicrobial peptide in the human innate immune system, is a 37-residue amphipathic alpha-helical cationic peptide released from the neutrophil granule precursor hCAP-18 by proteinase 3 cleavage at sites of infection, inflammation, and tissue injury [1, 2, 3]. The peptide possesses direct broad-spectrum antimicrobial activity against gram-positive and gram-negative bacteria, mycobacteria, enveloped viruses, and fungi through electrostatic binding to anionic microbial membranes followed by membrane permeabilization and lysis [4, 5]. In parallel, LL-37 functions as a pleiotropic immunomodulatory mediator, signaling through formyl peptide receptor 2 (FPR2/ALX) to recruit and activate innate immune cells [6], neutralizing lipopolysaccharide to suppress endotoxemia [7], promoting wound healing through epidermal growth factor receptor transactivation and angiogenesis [8], and modulating dendritic cell and T cell responses [9]. Expression of the CAMP gene encoding hCAP-18/LL-37 is transcriptionally upregulated by 1,25-dihydroxyvitamin D3 through a vitamin D response element, establishing a mechanistic link between vitamin D status and innate antimicrobial capacity that was demonstrated in the landmark Liu et al. (2006) study of toll-like receptor-triggered antimycobacterial defense [10].

The clinical evidence base for LL-37 as a therapeutic agent is most advanced in chronic wound healing. A first-in-human Phase I/II trial by Gronberg et al. (2014) demonstrated that topical synthetic LL-37 at 0.5 and 1.6 mg/mL enhanced healing of hard-to-heal venous leg ulcers with healing rate constants three- to six-fold greater than placebo and no safety concerns [11]. A Phase IIb multicenter trial by Mahlapuu et al. (2021) in 148 patients did not achieve significance in the full cohort but identified a statistically meaningful benefit in the subgroup with ulcers exceeding 10 cm² [12]. A randomized trial by Miranda et al. (2023) demonstrated that LL-37 cream enhanced healing of diabetic foot ulcers with mild infection [25]. In infectious disease, a randomized trial of oral recombinant LL-37 in *Lactococcus lactis* against SARS-CoV-2 Omicron BA.5.1.3 demonstrated significant shortening of viral clearance time with early intervention and acceptable safety [13].

LL-37 is also implicated in the pathogenesis of inflammatory skin diseases. In rosacea, aberrant processing of hCAP-18 by kallikrein 5 serine protease in facial skin generates elevated levels of LL-37 and modified cathelicidin fragments that

drive the characteristic inflammation and vasodilation [14]. In psoriasis, LL-37 complexed with self-DNA activates plasmacytoid dendritic cells through toll-like receptor 9, amplifying the type I interferon response that sustains the psoriatic plaque [15]. In cancer biology, LL-37 displays context-dependent effects: anti-tumorigenic activity through direct membrane disruption of cancer cells and immune cell recruitment in some models, and pro-tumorigenic activity through promotion of proliferation, angiogenesis, and metastasis in others, particularly in colorectal, breast, and lung cancers where tumor-associated macrophage-derived LL-37 activates Wnt/beta-catenin signaling [16, 17].

The principal pharmacokinetic limitation is rapid proteolytic degradation in biological fluids, with a serum half-life of minutes to hours, restricting systemic delivery and driving therapeutic development toward topical application, protease-resistant analogs (d-amino acid substitutions, cyclization, stapled peptides), and nanoparticle or hydrogel encapsulation [18, 19]. The compound is available as a research-grade synthetic peptide at greater than 95 percent purity. This monograph documents the complete identification, molecular pharmacology, preclinical and clinical evidence base, reconstitution and handling considerations, stack interactions, adverse events and pathogenic associations, and a comparative assessment against five alternative antimicrobial peptide candidates.

3. Discovery and Development History

3.1 Identification of the human cathelicidin gene

The cathelicidin gene family was identified across multiple mammalian species in the early 1990s, characterized by a conserved cathelin-like propiece domain and variable carboxy-terminal antimicrobial peptide domains. The human cathelicidin was independently identified by two groups. Agerberth, Gudmundsson, and colleagues at the Karolinska Institutet in Stockholm isolated a cDNA clone from a human bone marrow library encoding a cathelin-like precursor protein of 170 amino acid residues, from which they predicted a carboxy-terminal antimicrobial peptide initially designated FALL-39 (based on the first four amino acids phenylalanine-alanine-leucine-leucine and a predicted 39-residue length) [1]. The gene was designated CAMP (cathelicidin antimicrobial peptide) and mapped to chromosome 3p21.31. Cowland et al. independently identified the same protein from neutrophil-specific granule preparations and designated it hCAP-18 (human cationic antimicrobial protein of 18 kDa) [26].

3.2 Determination of the mature peptide

The mature processed form of the human cathelicidin was established by Gudmundsson et al. (1996), who demonstrated that the cathelin-like precursor is cleaved in granulocytes to release a 37-residue carboxy-terminal peptide beginning with the dipeptide leucine-leucine, which they designated LL-37 [2]. This established the nomenclature that has become universal in the antimicrobial peptide literature. Sorensen et al. (2001) subsequently identified proteinase 3, a serine protease stored in neutrophil azurophilic granules and released upon activation, as the specific protease responsible for the extracellular cleavage of hCAP-18 to LL-37 [3]. This finding established the two-compartment model: hCAP-18 is stored safely in inactive form within specific granules, and activation occurs extracellularly through proteinase 3 activity at the site of neutrophil degranulation.

3.3 Vitamin D transcriptional regulation

A transformative advance in the understanding of LL-37 biology came with the identification of a vitamin D response element (VDRE) in the CAMP gene promoter. Wang et al. (2004) first demonstrated that 1,25-dihydroxyvitamin D₃ directly induces CAMP gene transcription in human cell lines [27]. Liu et al. (2006), in a landmark paper in *Science*, demonstrated that toll-like receptor 2/1 activation of human macrophages by *Mycobacterium tuberculosis* lipopeptides triggers upregulation of both CYP27B1 (the enzyme that converts 25-hydroxyvitamin D to the active 1,25-dihydroxy form) and the vitamin D receptor, establishing an intracrine vitamin D signaling circuit that culminates in cathelicidin induction and intracellular killing of *M. tuberculosis* [10]. This finding provided a molecular mechanism for the long-observed epidemiological association between vitamin D deficiency and susceptibility to tuberculosis and other infections, and established the vitamin D-cathelicidin axis as a major research paradigm in innate immunity.

3.4 Expansion of the research literature

The subsequent two decades produced a research literature of extraordinary breadth. LL-37 was characterized as a multifunctional immunomodulatory peptide with activities extending far beyond direct antimicrobial killing: chemotaxis of immune cells through FPR2 [6], lipopolysaccharide neutralization [7], modulation of dendritic cell maturation [9], promotion of angiogenesis [8], enhancement of wound healing, and regulation of autophagy [28]. The peptide was also identified as a pathogenic factor in rosacea (Yamasaki et al. 2007, characterizing the kallikrein 5-mediated aberrant processing of cathelicidin in rosacea skin) [14] and in psoriasis (Lande et al. 2007, demonstrating LL-37-DNA complexes as activators of plasmacytoid dendritic cells) [15].

3.5 Clinical translation

Clinical development of LL-37 as a therapeutic agent began with Lipopeptide AB (later Pergamum AB, later ProMore Pharma), a Swedish biotechnology company that advanced topical synthetic LL-37 through a first-in-human Phase I/II trial in venous leg ulcers (Gronberg et al. 2014) [11] and a Phase IIb multicenter trial (Mahlpuu et al. 2021) [12]. The diabetic foot ulcer application was pursued independently by Miranda et al. (2023) at the University of Indonesia [25]. The oral recombinant LL-37 approach for systemic infectious disease was advanced by a

Chinese consortium through a randomized trial in SARS-CoV-2 (Zhao et al. 2023) [13]. As of the date of this monograph, LL-37 has not received regulatory approval in any jurisdiction as a pharmaceutical product. The compound is classified as an investigational drug in clinical wound healing and infectious disease applications.

4. Mechanism of Action

LL-37 is a multi-mechanism effector of innate immunity. Its biological activities divide into two principal categories: direct antimicrobial activity through membrane interaction and disruption, and indirect immunomodulatory activity through receptor-mediated signaling on host cells. Both categories operate at physiologically achievable concentrations at sites of neutrophil degranulation and epithelial secretion.

4.1 Direct antimicrobial activity

The direct antimicrobial mechanism of LL-37 begins with electrostatic attraction between the cationic peptide (net charge +6 at physiological pH) and the anionic outer surface of microbial membranes. Gram-negative bacteria present lipopolysaccharide (LPS) on the outer membrane leaflet; gram-positive bacteria present teichoic acids and lipoteichoic acids; fungal membranes present phosphatidylinositol and other anionic phospholipids. The selectivity for microbial over mammalian membranes arises from the asymmetric distribution of phospholipids in eukaryotic cell membranes, where anionic phosphatidylserine is sequestered in the inner leaflet and the outer leaflet is predominantly neutral (phosphatidylcholine and sphingomyelin), and from the membrane-stabilizing effect of cholesterol in mammalian membranes [4, 5].

Upon binding to the microbial membrane surface, LL-37 undergoes a conformational transition from disordered to alpha-helical, inserting the hydrophobic face of the amphipathic helix into the lipid bilayer. The mechanism of membrane disruption has been characterized by biophysical studies as a carpet model or toroidal pore model depending on peptide concentration and membrane composition [4, 21]. At lower peptide-to-lipid ratios, the peptides carpet the membrane surface in a parallel orientation, thinning and destabilizing the bilayer. At higher ratios, the peptides reorient perpendicular to the membrane plane and form toroidal pores in which peptide molecules and lipid headgroups together line the pore lumen, creating transmembrane channels that dissipate the electrochemical gradient, permit ion leakage, and ultimately cause osmotic lysis [21].

Neville et al. (2006) demonstrated by X-ray reflectivity and neutron reflectivity that LL-37 discriminates between bacterial-type and mammalian-type lipid headgroups, preferentially inserting into phosphatidylglycerol-containing monolayers (bacterial membrane mimics) over phosphatidylcholine monolayers (mammalian membrane mimics) [29]. Molecular dynamics simulations by Zhao et al. (2018) confirmed preferential insertion into POPG (palmitoyloleoylphosphatidylglycerol) bilayers over POPC (palmitoylcholinephosphatidylcholine) bilayers, consistent with the headgroup discrimination model [30].

The spectrum of direct antimicrobial activity encompasses gram-positive bacteria (*Staphylococcus aureus*, including methicillin-resistant strains; *Streptococcus pyogenes*; *Enterococcus faecalis*), gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Burkholderia pseudomallei*), mycobacteria (*Mycobacterium tuberculosis*, through the vitamin D-cathelicidin intracellular axis), fungi (*Candida albicans*, where LL-37 disrupts yeast and hyphal membranes) [31], and enveloped viruses (influenza, herpes simplex, HIV, SARS-CoV-2) through disruption of the viral envelope [32].

An additional intracellular target was identified by Chung et al. (2015), who demonstrated that LL-37 binds bacterial acyl carrier protein (AcpP) in the cytoplasm after membrane translocation, inhibiting fatty acid biosynthesis as a secondary bactericidal mechanism [33]. This finding suggests that the antimicrobial activity is not solely attributable to membrane disruption but includes intracellular target engagement.

4.2 Antibiofilm activity

LL-37 possesses activity against bacterial biofilms at concentrations below those required for planktonic killing. The antibiofilm mechanisms include inhibition of initial bacterial attachment to surfaces, disruption of quorum-sensing signaling, and promotion of twitching motility in *Pseudomonas aeruginosa* that disperses the biofilm architecture [34]. Memariani and Memariani (2023) reviewed the antibiofilm properties extensively and reported minimum biofilm inhibitory concentrations in the range of 0.5 to 16 micrograms per milliliter for clinically relevant pathogens [34]. The antibiofilm activity is therapeutically relevant for chronic wound infections, implant-associated infections, and cystic fibrosis lung disease, where biofilm-forming organisms are the dominant pathogenic mode.

4.3 Immunomodulatory receptor signaling

LL-37 engages multiple host cell receptors to produce immunomodulatory effects that extend far beyond direct antimicrobial killing.

Formyl peptide receptor 2 (FPR2/ALX/FPRL1): LL-37 is a chemotactic agonist for FPR2, a G-protein-coupled receptor expressed on neutrophils, monocytes, macrophages, and subsets of T cells [6]. Signaling through FPR2 produces chemotaxis of immune cells to sites of infection, degranulation of neutrophils, and calcium flux in monocytes. The LL-37-FPR2 axis is a principal mechanism by which the peptide recruits and activates the innate immune response beyond the initial neutrophil degranulation event. Sun et al. (2013) demonstrated that LL-37 induces synthesis and release of cysteinyl leukotrienes from human eosinophils through FPR2, linking cathelicidin signaling to the leukotriene inflammatory cascade [35].

Epidermal growth factor receptor (EGFR): LL-37 transactivates EGFR on epithelial cells and keratinocytes through a metalloproteinase-dependent mechanism that releases membrane-tethered EGFR ligands (heparin-binding EGF-like growth factor, amphiregulin). EGFR transactivation drives keratinocyte migration and proliferation, angiogenesis through vascular endothelial growth factor induction, and wound re-epithelialization [8]. This mechanism is the molecular basis for the wound-healing activity observed in clinical trials.

P2X7 receptor: LL-37 activates the P2X7 purinergic receptor on monocytes and macrophages, triggering NLRP3 inflammasome assembly, caspase-1 activation, and release of mature interleukin-1 beta and interleukin-18 [36]. This pathway amplifies the inflammatory response at sites of infection but can also contribute to excessive inflammation in sterile injury contexts.

Toll-like receptors: LL-37 modulates toll-like receptor signaling in complex, context-dependent ways. It can suppress TLR4-mediated inflammatory responses by sequestering LPS and preventing its presentation to CD14/TLR4 [7]. Conversely, it can enhance TLR3 signaling through FPRL1-dependent pathways [37] and, when complexed with self-DNA, can activate TLR9 on plasmacytoid dendritic cells, a mechanism central to psoriasis pathogenesis [15].

Lipopolysaccharide neutralization: LL-37 binds lipopolysaccharide with high affinity (dissociation constant in the nanomolar range) through electrostatic interaction between the cationic peptide and the anionic lipid A moiety of LPS [7]. This binding prevents LPS from engaging CD14 and TLR4 on monocytes and

macrophages, suppressing the downstream NF-kappaB-dependent inflammatory cascade and reducing tumor necrosis factor alpha, interleukin-6, and interleukin-1 beta release. The LPS-neutralizing activity is therapeutically relevant for gram-negative sepsis and endotoxemia.

4.4 Wound healing mechanisms

The wound-healing activity of LL-37 is a composite of multiple mechanisms: direct antimicrobial killing reduces the bioburden in chronic wounds; EGFR transactivation promotes keratinocyte migration and re-epithelialization; angiogenesis is stimulated through vascular endothelial growth factor induction; fibroblast migration and extracellular matrix remodeling are enhanced; and the immunomodulatory profile shifts the wound microenvironment from a chronically inflamed, non-healing state toward a resolution and repair phenotype [8, 38]. Xi et al. (2024) demonstrated that LL-37 promotes wound healing in diabetic mice by regulating TFEB-dependent autophagy in macrophages, shifting macrophage polarization from the M1 pro-inflammatory to the M2 pro-healing phenotype [28].

5. Pharmacokinetics

5.1 Endogenous levels

Circulating hCAP-18/LL-37 levels in healthy human plasma range from approximately 0.5 to 5.0 micrograms per milliliter (approximately 110 to 1100 nanomolar), with the majority present as the intact hCAP-18 precursor bound to lipoproteins and a smaller fraction as processed LL-37 [39]. At sites of active infection or inflammation, local LL-37 concentrations can reach 10 to 100 micrograms per milliliter (2.2 to 22 micromolar) in wound fluid, bronchoalveolar lavage, and abscess contents, reflecting the massive neutrophil degranulation that occurs at these sites [40].

Dixon et al. (2012) demonstrated a positive correlation between circulating hCAP-18/LL-37 levels and 25-hydroxyvitamin D levels in healthy adults, confirming the vitamin D transcriptional regulation *in vivo* [41]. Serum LL-37 levels are reduced in vitamin D-deficient individuals and can be partially restored by vitamin D supplementation [42].

5.2 Exogenous peptide behavior

Synthetic LL-37 applied topically to wound beds is absorbed locally and achieves high concentrations in the wound microenvironment. Systemic absorption from topical application is negligible at the doses used in clinical trials (0.5 to 3.2 mg/mL applied twice weekly) [11, 12].

The principal pharmacokinetic limitation of LL-37 as a systemic therapeutic agent is its rapid proteolytic degradation. The peptide is susceptible to cleavage by serum proteases, including neutrophil elastase, cathepsin G, proteinase 3, and matrix metalloproteinases. The serum half-life of native L-form LL-37 is estimated at 15 to 30 minutes in human serum *in vitro*, limiting the achievable systemic exposure from parenteral administration [18]. Stromstedt et al. (2009) demonstrated that d-enantiomer substitutions at protease-sensitive sites rendered LL-37-derived peptides resistant to proteolytic degradation, with the all-D enantiomer (D-LL-37) completely resistant to serum proteases while retaining antimicrobial activity [18].

5.3 Distribution

LL-37 is distributed primarily at mucosal surfaces and in tissues with high neutrophil traffic. The peptide is expressed constitutively in the skin (by keratinocytes in the stratum granulosum), in the gastrointestinal tract (by colonic epithelial cells), in the respiratory tract (by airway epithelial cells), in the urogenital tract, and in the salivary glands [43]. Induced expression occurs at sites of infection and inflammation through vitamin D-dependent and vitamin D-independent pathways (including butyrate and other short-chain fatty acids in the colonic epithelium) [44].

5.4 Metabolism and elimination

The primary route of inactivation is proteolytic degradation by endogenous serine proteases and metalloproteinases. The degradation products are small peptide fragments that are further processed to individual amino acids and enter normal amino acid metabolism. No hepatic cytochrome P450-mediated metabolism occurs; the pharmacokinetic behavior is entirely peptidase-driven.

Renal clearance of intact LL-37 is minimal owing to binding to plasma proteins and lipoproteins (apolipoprotein A-I in high-density lipoproteins is a major binding partner for circulating hCAP-18) and rapid proteolytic degradation before significant renal filtration occurs [39].

5.5 Routes of administration

Topical application to wound beds is the most advanced clinical route, using formulations of synthetic LL-37 in vehicle creams or hydrogels at concentrations of 0.5 to 3.2 mg/mL [11, 12, 25]. Oral delivery of recombinant LL-37 in *Lactococcus lactis* has been tested clinically for systemic infectious disease [13]. Parenteral (intravenous, subcutaneous) administration of native LL-37 is limited by proteolytic degradation and has not advanced to clinical trials; research applications use protease-resistant analogs, pegylated forms, or nanoparticle encapsulation for parenteral delivery [19]. Inhalational delivery for respiratory infection and cystic fibrosis has been explored preclinically but has not entered clinical testing.

6. Preclinical Pharmacology

6.1 Antimicrobial efficacy in vivo

LL-37 and its murine ortholog CRAMP have demonstrated efficacy in multiple infection models. CRAMP-knockout mice (Camp^{-/-}) show increased susceptibility to skin infection with group A Streptococcus, urinary tract infection with uropathogenic E. coli, and necrotizing fasciitis, demonstrating the non-redundant role of cathelicidin in host defense [45]. Administration of exogenous LL-37 rescues the susceptibility phenotype and reduces bacterial load in these models.

In a murine wound infection model, topical LL-37 reduced Staphylococcus aureus colony counts by approximately 2 log units and accelerated wound closure compared to vehicle control [38]. The antibiofilm activity was confirmed in vivo in a catheter-associated biofilm model, where LL-37 coating reduced Pseudomonas aeruginosa biofilm formation by greater than 90 percent [34].

6.2 Wound healing models

LL-37 accelerated wound closure in full-thickness excisional wound models in diabetic (db/db) mice and in aged mice, with effects on both re-epithelialization (EGFR-dependent) and granulation tissue formation (angiogenesis-dependent) [8, 28]. Xi et al. (2024) demonstrated that the mechanism in diabetic wound healing involves regulation of TFEB-dependent autophagy in wound macrophages, promoting M2 polarization and resolution of chronic inflammation [28]. Yang et al. (2020) reported that chitosan hydrogel encapsulation of LL-37 enhanced wound healing in a full-thickness burn model by providing sustained release and protection from proteolytic degradation [46].

6.3 Sepsis and endotoxemia models

Intravenous or intraperitoneal LL-37 administration reduced mortality in murine models of cecal ligation and puncture (CLP) sepsis and lipopolysaccharide-induced endotoxemia, with the protective effect attributable to LPS neutralization and mod-

ulation of the inflammatory cytokine response [7]. The anti-sepsis efficacy is dose-dependent, with optimal protection at doses that achieve local concentrations in the low micromolar range at the site of infection.

6.4 Tuberculosis models

The vitamin D-cathelicidin axis has been extensively studied in mycobacterial infection models. In human macrophage culture, vitamin D3 supplementation induces CAMP gene expression through the VDR-VDRE pathway and enhances intracellular killing of *Mycobacterium tuberculosis* in an LL-37-dependent manner [10]. In vivo, Camp-/- mice show modestly increased susceptibility to mycobacterial infection, though the murine CRAMP ortholog is less potent than human LL-37 against *M. tuberculosis* in vitro.

6.5 Anti-inflammatory and autoimmune models

LL-37 has been studied in models of inflammatory bowel disease, rheumatoid arthritis, and neuroinflammation. In dextran sulfate sodium-induced colitis, exogenous LL-37 reduced colonic inflammation and preserved epithelial barrier integrity [47]. In adjuvant-induced arthritis, LL-37 modulated synovial macrophage polarization and reduced joint swelling. The anti-inflammatory effects operate through LPS neutralization, suppression of NF-kappaB activation, and promotion of anti-inflammatory cytokine release (interleukin-10, transforming growth factor beta).

6.6 Cancer models

The cancer pharmacology of LL-37 is context-dependent and tumor type-specific. Anti-tumorigenic activity has been reported in gastric cancer, colon cancer (at low concentrations), and pancreatic cancer, where LL-37 induces apoptosis and suppresses autophagy [48]. Pro-tumorigenic activity has been reported in ovarian cancer, breast cancer, and lung cancer, where LL-37 promotes proliferation through EGFR transactivation, enhances angiogenesis, and supports tumor-associated macrophage-driven immunosuppression [16, 17]. Ji et al. (2019) demonstrated that myeloid cell-derived LL-37 promotes lung cancer growth by activating Wnt/beta-catenin signaling in a FPRL1-dependent manner [17]. The dual cancer pharmacology cautions against simplistic interpretation of LL-37 as uniformly anti-neoplastic.

7. Clinical Evidence Base

7.1 Chronic wound healing: venous leg ulcers

The most advanced clinical development is in chronic wound healing. Gronberg et al. (2014) reported the first-in-human Phase I/II randomized, double-blind, placebo-controlled trial of topical synthetic LL-37 in 34 patients with hard-to-heal venous leg ulcers [11]. After a 3-week placebo run-in period, patients received twice-weekly applications of LL-37 at 0.5, 1.6, or 3.2 mg/mL or placebo for 4 weeks, followed by a 4-week follow-up. The 0.5 mg/mL dose produced healing rate constants approximately six-fold greater than placebo; the 1.6 mg/mL dose produced rate constants approximately three-fold greater. Mean ulcer area decreased by 68 percent and 50 percent at the 0.5 and 1.6 mg/mL doses, respectively. The highest dose (3.2 mg/mL) did not produce benefit, suggesting an inverted-U dose-response relationship consistent with concentration-dependent self-association, excessive inflammatory signaling at high concentrations, or local cytotoxicity at supraphysiological peptide levels. There were no safety concerns regarding local or systemic adverse events.

Mahlapuu et al. (2021) conducted a Phase IIb multicenter, prospective, randomized, double-blind, placebo-controlled trial in 148 patients with hard-to-heal venous leg ulcers across 14 centers in Poland and Sweden [12]. Patients received LL-37 in combination with compression therapy for 13 weeks. The primary endpoint in the full cohort was not met; however, pre-specified subgroup analysis of patients with larger ulcers (greater than or equal to 10 cm²) showed statistically significant improvements in multiple wound healing endpoints. The treatment was well tolerated with no safety concerns. The authors concluded that LL-37 may offer treatment benefit specifically in patients with large ulcers, warranting further investigation in this enriched population.

7.2 Diabetic foot ulcers

Miranda et al. (2023) reported a randomized, double-blind, controlled trial of LL-37 cream in enhancing healing of diabetic foot ulcers with mild infection in 60 patients at the University of Indonesia [25]. LL-37 cream applied to diabetic foot ulcers

enhanced the healing rate with consistent increases in granulation tissue formation across measurement intervals. The treatment was well tolerated with no adverse events attributable to the study medication.

7.3 SARS-CoV-2 infection

Zhao et al. (2023) reported a randomized, placebo-controlled trial of recombinant LL-37 produced in *Lactococcus lactis* as an oral antiviral agent in 238 hospitalized adults with SARS-CoV-2 Omicron BA.5.1.3 infection [13]. The primary endpoint was negative conversion time (NCT) of SARS-CoV-2 RNA. Early intervention (within 6 days of symptom onset) significantly shortened NCT (LL-37 group 9.80 plus or minus 2.67 days versus placebo 14.04 plus or minus 5.89 days, p less than 0.01). The adjusted hazard ratio for viral clearance with early treatment was 6.27-fold higher than with 7-day-delayed intervention. No severe adverse events were observed during hospitalization or follow-up. This trial represents the first clinical demonstration of recombinant LL-37 as a systemic anti-infective agent.

7.4 Vitamin D and cathelicidin in tuberculosis

The vitamin D-cathelicidin axis has been studied clinically in tuberculosis. Mily et al. (2013) demonstrated that oral phenylbutyrate with or without vitamin D3 supplementation upregulated cathelicidin LL-37 expression in human macrophages *ex vivo* [49]. Rekha et al. (2018) reported that combined phenylbutyrate and vitamin D3 supplementation as adjunctive therapy in drug-sensitive pulmonary tuberculosis enhanced immune responses including cathelicidin expression, suggesting a host-directed therapy approach [50]. These studies support the concept of inducing endogenous LL-37 production through vitamin D supplementation rather than administering exogenous peptide.

7.5 Rosacea pathogenesis

LL-37 is a pathogenic mediator in rosacea rather than a therapeutic agent. Yamasaki et al. demonstrated that rosacea skin contains elevated levels of cathelicidin peptides and that the serine protease kallikrein 5 (KLK5) is upregulated in rosacea, producing aberrant processing of hCAP-18 to generate LL-37 fragments with enhanced pro-inflammatory activity [14]. Injection of LL-37 fragments into mouse skin reproduces rosacea-like inflammation. Two et al. (2014) reviewed the kallikrein 5-mediated cathelicidin processing pathway in rosacea pathogenesis and

its implications for therapeutic targeting [51]. This pathogenic role must be considered in any systemic or dermatologic application of LL-37: exogenous administration to facial skin could exacerbate rosacea.

7.6 Psoriasis pathogenesis

Lande et al. (2007) demonstrated that LL-37 released from damaged keratinocytes in psoriatic skin forms complexes with self-DNA, and that these LL-37-DNA complexes are internalized by plasmacytoid dendritic cells and activate toll-like receptor 9 in the endosomal compartment, triggering interferon-alpha production and sustaining the type I interferon response that drives psoriatic plaque formation [15]. This finding established LL-37 as a bridge between innate antimicrobial defense and autoimmune pathology, converting innocuous self-DNA into a danger signal through complex formation with the cationic peptide.

8. Sourcing and Quality Verification

Synthetic LL-37 is the primary research-grade material. The peptide is commercially available from multiple peptide synthesis companies at purities of greater than 95 percent (HPLC area percent). Principal suppliers include AnaSpec (catalog AS-61302), Bachem, GenScript, Tocris (catalog 4561), Sigma-Aldrich/Merck, Phoenix Pharmaceuticals, InvivoGen (catalog tlr1-l37), and multiple custom peptide synthesis services.

Investigators should confirm compound identity and purity on every research-grade lot through:

- Reversed-phase HPLC area-percent purity, ideally greater than 95 percent, with greater than 98 percent preferred for quantitative pharmacology studies
- Electrospray ionization mass spectrometry confirmation of molecular weight (expected $[M+H]^+$ at 4494.33 for the free acid form; deconvoluted mass 4493.33 Da)
- Amino acid analysis to confirm composition and absence of deletion or truncation products
- Endotoxin testing (Limulus amebocyte lysate assay) to confirm endotoxin levels below 0.1 endotoxin units per microgram of peptide, critical for immunological studies where LPS contamination would confound interpretation
- Trifluoroacetate (TFA) counterion content determination; synthetic peptides are typically supplied as TFA salts, and the TFA content (approximately 15 to 20 percent by weight) must be accounted for in dose calculations

Recombinant LL-37 produced in bacterial or yeast expression systems requires additional verification of correct folding and absence of host-cell protein contamination. The *Lactococcus lactis* expression system used in the Zhao et al. (2023) clinical trial employed a food-grade organism with established safety profile [13].

Pricing for synthetic LL-37 at the time of monograph preparation ranges from approximately \$200 per milligram at greater than 95 percent purity to \$600 per milligram at greater than 98 percent purity, depending on supplier and quantity. The cost per dose for topical wound healing applications (0.5 to 1.6 mg/mL in 1 to 5 mL

application volumes) is approximately \$100 to \$3000 per treatment, a significant limitation for broad clinical adoption that has driven interest in recombinant production and in shorter synthetic analogs.

9. Reconstitution and Handling

LL-37 is supplied as a lyophilized powder and should be stored desiccated at minus 20 degrees Celsius or below for long-term storage. Under these conditions, the peptide is stable for at least 2 years from the date of manufacture.

For reconstitution, dissolve the lyophilized peptide in sterile, endotoxin-free water to a stock concentration of 1 to 5 mg/mL (approximately 220 to 1110 micromolar). Vortex gently and allow to dissolve fully; brief sonication in a water bath (5 to 10 minutes at room temperature) may assist dissolution. Do not use strongly acidic or basic reconstitution buffers; the peptide is stable at pH 4 to 8. Dimethyl sulfoxide may be used for stock solutions at higher concentrations (up to 20 mg/mL) for in vitro applications where DMSO vehicle is acceptable.

Aliquot the reconstituted stock solution into single-use volumes to avoid repeated freeze-thaw cycles. Store aliquots at minus 20 degrees Celsius for use within 6 months or at minus 80 degrees Celsius for longer storage. The peptide retains greater than 90 percent activity through at least 3 freeze-thaw cycles, but single-use aliquoting is recommended for quantitative studies.

Working dilutions should be prepared in the assay buffer or vehicle immediately before use. LL-37 adsorbs to polystyrene and polypropylene surfaces; use of low-binding microcentrifuge tubes and pipette tips is recommended for solutions below 10 micromolar to minimize surface losses. For in vitro antimicrobial assays, prepare dilutions in appropriate microbiological media (Mueller-Hinton broth, RPMI 1640) and note that LL-37 activity is inhibited by physiological salt concentrations (150 mM NaCl reduces antimicrobial activity by approximately 50 to 80 percent) and by serum proteins [5]. Assay conditions should be standardized and reported to enable cross-study comparisons.

For topical wound-healing applications, LL-37 is formulated in hydrogel or cream vehicles. The clinical trials used proprietary formulations; for laboratory research, incorporation into chitosan hydrogels, sodium alginate/gelatin hydrogels, or polyethylene glycol-polypropylene sulfide nanomicelles has been reported [46, 52].

Light protection is not required for routine handling but is reasonable practice for long-term storage. Avoid exposure to oxidizing agents; the methionine residue is susceptible to oxidation, which reduces antimicrobial activity.

10. Stack Interactions and Combinations

Investigators conducting research with LL-37 in combination with other compounds should consider:

Vitamin D3 (cholecalciferol) and 1,25-dihydroxyvitamin D3: Vitamin D is the principal transcriptional inducer of endogenous LL-37 production through the CAMP gene VDRE [10, 27]. Co-administration of vitamin D with exogenous LL-37 produces additive effects on antimicrobial defense through both endogenous induction and exogenous supplementation. Phenylbutyrate acts as an additional inducer of CAMP transcription through histone deacetylase inhibition and has been studied in combination with vitamin D in tuberculosis [49, 50].

Conventional antibiotics: LL-37 has demonstrated additive and in some cases synergistic activity with conventional antibiotics, including beta-lactams, fluoroquinolones, aminoglycosides, and colistin. The synergy is attributable to LL-37-mediated membrane permeabilization facilitating antibiotic entry into bacterial cells that would otherwise be impermeable [53]. Combination with antibiotics may permit dose reduction of both agents and is a rational strategy for biofilm-associated infections where neither agent alone achieves adequate efficacy.

Other antimicrobial peptides: Combination with defensins (HNP-1, HBD-2, HBD-3), lactoferricin, or lysozyme produces additive to synergistic antimicrobial activity, reflecting the natural co-expression of these peptides at mucosal surfaces [54]. The combination of LL-37 with lysozyme is particularly well characterized; lysozyme degrades peptidoglycan, exposing the cytoplasmic membrane to LL-37 attack.

Sodium chloride and divalent cations: Physiological salt concentrations (150 mM NaCl) and divalent cations (calcium, magnesium at millimolar concentrations) substantially inhibit the antimicrobial activity of LL-37 by screening the electrostatic interaction between the cationic peptide and anionic membrane surfaces [5]. This salt sensitivity is a major consideration for in vitro assay design and for clinical applications in body fluids with physiological electrolyte concentrations.

Serum and plasma proteins: Serum proteins, particularly apolipoprotein A-I in high-density lipoproteins, bind LL-37 and reduce its free concentration and antimicrobial activity [39]. Albumin binding also reduces effective concentration. In vitro antimicrobial assays performed in the presence of serum typically show 4- to 16-fold increases in minimum inhibitory concentrations compared to serum-free conditions.

Glycosaminoglycans: Heparin, heparan sulfate, and other polyanionic glycosaminoglycans bind LL-37 through electrostatic interaction and neutralize its antimicrobial and immunomodulatory activities [55]. Glycosaminoglycan-rich wound environments may therefore partially inhibit exogenous LL-37 activity.

Immunosuppressive agents: Corticosteroids suppress CAMP gene transcription and reduce endogenous LL-37 production. Concurrent corticosteroid use may partially offset the effects of exogenous LL-37 supplementation by reducing the endogenous contribution.

EGFR inhibitors: Since LL-37 wound-healing activity depends in part on EGFR transactivation, concurrent EGFR tyrosine kinase inhibitors (erlotinib, gefitinib) or anti-EGFR monoclonal antibodies (cetuximab) may attenuate the wound-healing effect. Conversely, in tumor contexts where LL-37-mediated EGFR transactivation contributes to tumor growth, EGFR inhibition may mitigate the pro-tumorigenic effect of endogenous LL-37.

11. Adverse Events and Safety Signal

11.1 Clinical safety data

The safety profile of exogenous LL-37 in clinical trials has been favorable. In the Gronberg et al. (2014) Phase I/II venous leg ulcer trial, there were no safety concerns regarding local or systemic adverse events at any of the three doses tested (0.5, 1.6, 3.2 mg/mL) [11]. The Mahlapuu et al. (2021) Phase IIb trial in 148 patients confirmed the tolerability with no drug-related serious adverse events [12]. The Miranda et al. (2023) diabetic foot ulcer trial reported no adverse events attributable to the study medication [25]. The Zhao et al. (2023) oral LL-37 trial in 238 SARS-CoV-2 patients reported no severe adverse events during hospitalization or follow-up [13].

11.2 Potential adverse effects

Despite the favorable clinical safety data at the doses and durations studied, several potential adverse effects warrant consideration:

Local inflammatory reactions: At supraphysiological concentrations, LL-37 can activate the P2X7 receptor and NLRP3 inflammasome, producing interleukin-1 beta release and local inflammation [36]. The inverted-U dose-response observed in the Gronberg et al. (2014) trial (no benefit at the highest 3.2 mg/mL dose) may reflect this excessive inflammatory activation.

Mast cell degranulation: LL-37 activates mast cells through MrgX2 (Mas-related G-protein-coupled receptor X2), producing degranulation, histamine release, and potential urticaria at the application site [56]. This effect is concentration-dependent and is more pronounced at supraphysiological concentrations.

Erythema and pain at application site: Mild local erythema and transient pain have been reported in some wound healing studies, consistent with the pro-inflammatory mechanisms at high local concentrations.

11.3 Pathogenic associations

Rosacea: Elevated cathelicidin and aberrant LL-37 processing by kallikrein 5 are central to rosacea pathogenesis [14]. Exogenous LL-37 application to rosacea-prone facial skin would be expected to exacerbate the condition. Systemic administration or topical application to non-facial sites does not carry the same risk, as the kallikrein 5 upregulation is tissue-specific.

Psoriasis: LL-37-DNA complexes activate plasmacytoid dendritic cells and sustain the type I interferon response in psoriatic skin [15]. Systemic elevation of LL-37 levels could theoretically exacerbate psoriasis in susceptible individuals, though this has not been observed in clinical trials to date.

Pro-tumorigenic effects: In certain cancers (ovarian, breast, lung, colorectal), LL-37 promotes tumor growth through EGFR transactivation, Wnt/beta-catenin signaling, and enhancement of tumor angiogenesis [16, 17]. Chronic elevation of LL-37 levels in patients with established malignancies of these types warrants caution, though the clinical significance of exogenous LL-37 at wound-healing doses on distant tumor biology is unknown.

11.4 Hemolytic activity

LL-37 produces dose-dependent hemolysis of human erythrocytes at concentrations above approximately 25 to 50 micrograms per milliliter (5.5 to 11 micromolar), reflecting the peptide's capacity to disrupt eukaryotic membranes at high concentrations despite the selectivity for anionic microbial membranes at lower concentrations [5]. The therapeutic index (ratio of hemolytic concentration to minimum inhibitory concentration) is approximately 10- to 50-fold for most bacterial pathogens, providing a reasonable but not unlimited safety margin. Parenteral administration at doses that would achieve systemic concentrations approaching the hemolytic threshold is contraindicated.

11.5 Immunogenicity

LL-37 is a self-peptide and is not expected to be immunogenic in most individuals. However, autoantibodies against LL-37 have been detected in patients with systemic lupus erythematosus and in some patients with psoriasis, raising the possi-

bility that chronic exogenous administration could, in theory, break tolerance in genetically susceptible individuals. No anti-drug antibody responses have been reported in the clinical trials conducted to date.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five antimicrobial and immunomodulatory peptide candidates against LL-37, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five candidates were selected as the principal peptide-based antimicrobial and immunomodulatory agents with substantive research programs that overlap with the LL-37 therapeutic space.

12.1 Human Beta-Defensin 3 (HBD-3)

Mechanism: HBD-3 is a 45-residue cationic antimicrobial peptide of the beta-defensin family, expressed constitutively in epithelial tissues and inducibly in response to infection and inflammation. Unlike LL-37's alpha-helical structure, HBD-3 adopts a beta-sheet-stabilized fold constrained by three intramolecular disulfide bonds. HBD-3 possesses broad-spectrum antimicrobial activity including against methicillin-resistant *Staphylococcus aureus* and is unique among beta-defensins in retaining activity at physiological salt concentrations [57].

Novelty: Moderate. The beta-defensin mechanism is well established and HBD-3 has been studied extensively since its identification in 2001.

Effect size: HBD-3 has antimicrobial potency comparable to or greater than LL-37 against gram-positive bacteria, with minimum inhibitory concentrations in the 1 to 4 microgram per milliliter range against MRSA. Anti-biofilm activity is modest compared to LL-37. Immunomodulatory effects include chemotaxis of dendritic cells and T cells through CCR6 and enhancement of adaptive immune responses, but the immunomodulatory repertoire is narrower than LL-37's multi-receptor signaling profile [57].

Promising potential: Moderate. No clinical trials have been conducted with exogenous HBD-3. Research remains preclinical. The three-disulfide-bond structure complicates chemical synthesis and increases manufacturing cost compared to the linear LL-37.

Side-effect profile: Preclinical only. Hemolytic activity is lower than LL-37 at equivalent concentrations, suggesting a potentially wider therapeutic index. No human safety data exist.

Overall validation: Low to moderate. Extensive preclinical characterization but no clinical translation.

Comparison to LL-37: HBD-3 has the advantage of salt resistance and lower hemolytic activity but lacks the multi-receptor immunomodulatory profile of LL-37, the clinical development history, and the structural simplicity (linear versus disulfide-constrained) that favors scalable synthesis. LL-37 is more advanced in clinical translation by a substantial margin.

12.2 Pexiganan (MSI-78)

Mechanism: Pexiganan is a 22-residue synthetic analog of magainin 2, an antimicrobial peptide originally isolated from the skin of the African clawed frog *Xenopus laevis*. The peptide adopts an amphipathic alpha-helical structure similar to LL-37 and kills bacteria through membrane disruption. Pexiganan has broad-spectrum activity against gram-positive and gram-negative bacteria including drug-resistant strains [58].

Novelty: Low. Pexiganan was developed in the 1990s and represents an early-generation antimicrobial peptide therapeutic.

Effect size: In Phase 3 clinical trials for diabetic foot ulcer infection (Lipsky et al. 2008), topical pexiganan 1 percent cream produced clinical cure rates of 85 to 90 percent, non-inferior to oral ofloxacin, the active comparator [58]. The FDA rejected the original new drug application (1999) on the grounds that non-inferiority to ofloxacin alone was insufficient without a placebo-controlled demonstration of superiority to vehicle. A subsequent reformulated Phase 3 trial was completed but results have not led to regulatory approval.

Promising potential: Low. Despite two cycles of Phase 3 development, pexiganan has not received FDA approval. The regulatory history illustrates the challenges of antimicrobial peptide drug development for topical infection indications.

Side-effect profile: Topical pexiganan was well tolerated in Phase 3 trials with no significant local or systemic adverse events. The safety profile is favorable for topical application.

Overall validation: Moderate. Pexiganan has the most extensive clinical trial history of any antimicrobial peptide therapeutic (two complete Phase 3 programs) but has failed to achieve regulatory approval.

Comparison to LL-37: Pexiganan is a simpler, shorter peptide with a narrower mechanism (direct antimicrobial activity without the immunomodulatory repertoire of LL-37). LL-37 has the advantage of the multi-functional immunomodulatory profile, the wound-healing promotion through EGFR transactivation, and the vitamin D transcriptional regulation that connects it to host immune status. Pexiganan has the advantage of a more extensive clinical trial database, lower cost of synthesis (22 versus 37 residues), and demonstrated non-inferiority to conventional antibiotics in Phase 3.

12.3 Omiganan (MBI-226, CLS001)

Mechanism: Omiganan is a 12-residue synthetic cationic peptide derived from indolicidin, an antimicrobial peptide originally isolated from bovine neutrophil cytoplasmic granules. The peptide has broad-spectrum antimicrobial activity against bacteria and fungi and is formulated as a topical agent for skin infections and catheter-associated infections [59].

Novelty: Low. The indolicidin-derived scaffold is well established and omiganan represents an optimized clinical candidate from the 1990s development era.

Effect size: In a Phase 3 trial for catheter-related infection prevention, topical omiganan 1 percent gel did not meet the primary endpoint of reduction in catheter colonization compared to povidone-iodine [59]. In Phase 2 trials for rosacea (topical omiganan 2.5 percent gel), the compound reduced inflammatory lesions but did not achieve statistical significance on all endpoints. Phase 3 development for rosacea was pursued by Cutanea Life Sciences (later Mayne Pharma) with mixed results.

Promising potential: Low to moderate. The compound has been through multiple clinical trial cycles with mixed results. It is available as a research tool but is not approved as a pharmaceutical product.

Side-effect profile: Topical omiganan was well tolerated with mild local irritation as the principal adverse event.

Overall validation: Low to moderate. Extensive clinical trial history but no regulatory approval and mixed efficacy results across multiple indications.

Comparison to LL-37: Omiganan is a shorter, simpler peptide with predominantly direct antimicrobial activity and limited immunomodulatory function. LL-37 has the advantage of the complete immunomodulatory repertoire, wound-healing activity, and the endogenous biology that connects it to host defense physiology. Omiganan has the advantage of smaller size, lower synthesis cost, and potentially better tissue penetration for topical applications.

12.4 Brilacidin (PMX-30063)

Mechanism: Brilacidin is a synthetic small-molecule defensin mimetic developed by Innovation Pharmaceuticals (formerly Cellceutix). It is not a peptide but a non-peptidic arylamide foldamer that mimics the amphipathic cationic structure of defensin antimicrobial peptides, producing membrane disruption of bacterial cells through a defensin-like mechanism [60]. The non-peptidic structure confers resistance to proteolytic degradation, addressing the principal pharmacokinetic limitation of native antimicrobial peptides including LL-37.

Novelty: High. Brilacidin represents a mechanistically novel approach: a small-molecule mimetic of the antimicrobial peptide mechanism that avoids the pharmacokinetic limitations of peptide therapeutics.

Effect size: In a Phase 2 trial for acute bacterial skin and skin structure infections (ABSSSI), intravenous brilacidin at 0.6 mg/kg produced clinical response rates non-inferior to daptomycin, the active comparator [60]. A Phase 2 trial for oral mucositis in cancer patients receiving chemoradiation demonstrated significant reduction in severe mucositis. Antiviral activity against SARS-CoV-2 was demonstrated in vitro and an investigator-initiated Phase 2 trial was completed.

Promising potential: Moderate to high. Brilacidin has produced positive Phase 2 results in multiple indications and represents the most pharmacokinetically viable approach to antimicrobial peptide-like therapy through its non-peptidic, protease-resistant structure.

Side-effect profile: Phase 2 trials have demonstrated tolerability with no dose-limiting toxicities. The non-peptidic structure eliminates the immunogenicity concerns associated with peptide therapeutics.

Overall validation: Moderate. Positive Phase 2 results in ABSSSI and oral mucositis, with Phase 3 development pending. The strongest clinical validation of a defensin-mimetic approach to date.

Comparison to LL-37: Brilacidin addresses LL-37's principal limitation (proteolytic instability) through its non-peptidic structure and is suitable for systemic intravenous administration. However, it lacks the immunomodulatory receptor signaling (FPR2, EGFR transactivation, TLR modulation) that gives LL-37 its multifunctional biological profile. The comparison highlights the fundamental trade-off between pharmacokinetic viability and biological complexity: brilacidin is pharmacokinetically superior but biologically simpler; LL-37 is biologically richer but pharmacokinetically limited.

12.5 Nisin

Mechanism: Nisin is a 34-residue lantibiotic (lanthionine-containing antimicrobial peptide) produced by *Lactococcus lactis*, approved as a food preservative (E234) by the European Union and generally recognized as safe (GRAS) by the FDA. Nisin kills gram-positive bacteria through a dual mechanism: binding to lipid II (the peptidoglycan biosynthesis precursor) and pore formation in the bacterial membrane [61]. The lipid II binding provides a target-specific component absent from the nonspecific electrostatic mechanism of LL-37.

Novelty: Low in the food-preservation context (used since the 1950s); moderate in the therapeutic antimicrobial context where repurposing as a clinical anti-infective is being explored.

Effect size: Nisin has potent activity against gram-positive bacteria including MRSA, vancomycin-resistant enterococci, and *Clostridioides difficile*, with minimum inhibitory concentrations in the 0.5 to 8 microgram per milliliter range [61]. Activity against gram-negative bacteria is limited owing to the outer membrane barrier that prevents access to lipid II, though combination with chelating agents (EDTA) or outer membrane-permeabilizing peptides (such as polymyxin B nonapeptide) extends the gram-negative spectrum.

Promising potential: Moderate. Clinical trials of nisin as a therapeutic antimicrobial are limited but active. The GRAS status and decades of food-safety data provide a safety foundation that de-risks clinical development. Topical nisin formulations for skin infections and wound healing are under investigation.

Side-effect profile: Nisin has an exceptional safety record in the food-preservation context, with no significant adverse events reported over decades of widespread use. The lantibiotic structure is resistant to gastrointestinal proteases, sup-

porting oral bioavailability for gastrointestinal infections.

Overall validation: Moderate. Extensive food-safety validation and strong pre-clinical antimicrobial data; limited therapeutic clinical data.

Comparison to LL-37: Nisin has the advantage of a target-specific mechanism (lipid II binding), protease resistance (lanthionine rings protect against proteolysis), and an exceptional safety record. LL-37 has the advantage of broad-spectrum activity including gram-negative bacteria and fungi, the immunomodulatory repertoire, and the wound-healing biology. The two peptides are complementary rather than directly competitive: nisin for gram-positive-dominant infections and LL-37 for the broader host-defense and wound-healing applications.

12.6 Comparator summary

The five compounds span distinct niches in the antimicrobial and immunomodulatory peptide landscape. **HBD-3** is a complementary endogenous defensin with salt resistance but no clinical development. **Pexiganan** has the most extensive Phase 3 clinical history but has not achieved approval and lacks immunomodulatory activity. **Omiganan** has a mixed clinical record across multiple indications. **Brilacidin** represents the most pharmacokinetically viable approach through its non-peptidic defensin-mimetic structure, with positive Phase 2 results. **Nisin** offers target-specific lipid II binding and an exceptional safety foundation from decades of food use.

LL-37 occupies a unique position in this landscape as the sole human cathelicidin, distinguished by its pleiotropic immunomodulatory profile (FPR2, EGFR, P2X7, TLR modulation, LPS neutralization), its wound-healing biology, its vitamin D transcriptional regulation, and its clinical development in chronic wounds and infectious disease. The principal limitations relative to the comparators are proteolytic instability (addressed by brilacidin's non-peptidic approach and by d-amino acid and nanoparticle strategies in the LL-37 analog field), high synthesis cost (addressed by recombinant production), and the concentration-dependent pathogenic associations in rosacea and psoriasis that require careful dose and route selection. Among the comparators evaluated, LL-37 has the broadest biological repertoire and the most direct translational relevance as a human endogenous peptide; it is the only candidate whose therapeutic development can leverage the endogenous vitamin D-cathelicidin induction pathway as a complementary or alternative strategy to exogenous peptide administration.

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This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly. LL-37 is not approved by any regulatory authority as a pharmaceutical product. The compound is available as a research-grade synthetic peptide; investigators should obtain analytical confirmation of identity, purity, and endotoxin content on every lot. The pathogenic associations of LL-37 in rosacea and psoriasis warrant consideration in clinical research design; exogenous administration to facial skin or systemic administration in patients with active autoimmune dermatologic disease should be approached with caution.