CLINICAL LEARNING GUIDE

LL-37

Cathelicidin | The Human Antimicrobial Peptide

Innate Immunity, Gut Barrier, and Tissue Repair — Mechanisms, Evidence, and Clinical Applications

Based on lecture and slide materials by William Seeds, MD — SSRP Institute | Cellular Medicine Education

SECTION 1 · PROFILE OF THE PEPTIDE

Overview

LL-37 is the only human cathelicidin — a 37-amino-acid, cationic (net charge +6), amphipathic α-helical antimicrobial peptide released from its precursor hCAP18 by proteinase-3 cleavage. It is made by neutrophils, monocytes, epithelial cells, and NK cells, and — importantly for this category — cathelicidins are produced mainly in the large bowel, where LL-37 serves as the gut's principal natural antimicrobial. It is genuinely pleiotropic: a single molecule that is antimicrobial, anti-biofilm, immunomodulatory, pro-wound-healing/angiogenic, and (context-dependently) anti-cancer.

LL-37 appears in two categories in this work. It was introduced earlier among the immune-regulation peptides; here it is framed for recovery and gut stabilization, because in the gut its broad antimicrobial action (against infection, dysbiosis, biofilm) combines with its barrier-supporting and immunomodulatory effects to address exactly the problems that arise when the gut barrier breaks down — infection, dysbiosis, and the immune dysregulation that follows. The single most important practical fact about LL-37 is that it is vitamin-D-dependent: vitamin D drives LL-37 transcription, so without adequate vitamin D status the peptide is largely ineffective. Optimizing vitamin D is therefore step one — and often a therapy in its own right.

Peptide Profile

Property	Detail
Name	LL-37 (cathelicidin; the human antimicrobial peptide)
Structure	37 amino acids; net charge +6; cationic, amphipathic α-helix
Origin	Released from precursor hCAP18 by proteinase-3 cleavage; the only human cathelicidin
Where made	Neutrophils, monocytes, epithelial cells, NK cells — cathelicidins predominantly in the large bowel
Functions	Antimicrobial, anti-biofilm, immunomodulatory, wound-healing/angiogenic, context-dependent anti-cancer
Key regulator	Vitamin D — $1,25(OH)_2D_3$ / VDR drives LL-37 transcription (status is rate-limiting)

Property	Detail
Routes (investigational)	Subcutaneous, topical/site-specific, intratumoral (melanoma trial), IV (sepsis models)
Regulatory	Not FDA-approved; investigational; Phase I (melanoma, intratumoral)

Where LL-37 Sits

LL-37 is the innate-immune/antimicrobial member of this recovery and gut-stabilization group, and it complements the others by working on the infection/biofilm and immune-modulation side of gut health rather than purely on the barrier (Larazotide) or mucosal repair (BPC-157, GHK-Cu) or NF-κB-driven inflammation (KPV). In the gut it is most relevant for dysbiosis, biofilm-associated and drug-resistant infection, SIBO with candida overgrowth, and H. pylori contexts, while its immunomodulatory arm (sequestering LPS, calming TLR4 signaling) helps restrain the inflammation that accompanies a leaky, dysbiotic gut. Because its activity depends on vitamin D, it pairs naturally with vitamin D optimization.

> ⚠ **LL-37 is not FDA-approved (investigational). Two boundaries are critical: it has CONTEXT-DEPENDENT cancer effects (anti-tumor in some cancers, but pro-tumorigenic in lung, breast, and ovarian cancer), and it can EXACERBATE autoimmune disease — avoid in psoriasis and lupus, where LL-37 is already elevated and drives inflammasome/pDC activation. And it is vitamin-D-dependent: optimize vitamin D first, or LL-37 will be largely ineffective.**

SECTION 2 · MODES OF ACTION AND MECHANISMS

LL-37 is pleiotropic by design — it engages several signaling axes in parallel, and which effects dominate depends on tissue context, peptide concentration, and which receptors the local cells express. For the gut, three arms matter most: direct antimicrobial action, immunomodulation (especially LPS neutralization), and tissue repair.

1. Direct Antimicrobial / Anti-Biofilm Action

As a cationic, amphipathic peptide, LL-37 is drawn to the negatively charged surfaces of microbes. It interacts with LPS on Gram-negative membranes, oligomerizes into tetrameric channels (around 25 μM), and forms pores in unsaturated-phospholipid membranes — killing the organism. Its spectrum is broad (Gram-positive, Gram-negative, fungi, viruses), it works on drug-resistant strains, and — strikingly — it disrupts biofilms at concentrations far below the killing MIC (e.g., P. aeruginosa biofilm at 0.5 μg/mL, ~128× below MIC). It also kills intracellular S. aureus inside macrophages and synergizes with conventional antibiotics. Resistance development against LL-37 is very low.

2. Immunomodulation (the Gut/Sepsis Arm)

- **LPS sequestration / TLR4:** LL-37 binds and neutralizes LPS (endotoxin), blocking TLR4 signaling — a key way it calms the inflammation driven by a leaky, dysbiotic gut. In rat sepsis models, 1 mg/kg IV reduced lethality, endotoxin, and TNF-α comparably to polymyxin B.
- **Cytokine & cell-death modulation:** it suppresses pro-inflammatory cytokines and macrophage pyroptosis, while enhancing neutrophil extracellular traps (NETs) and ectosome release to trap and kill microbes.

- **Receptor engagement:** acts through receptors including FPRL1/FPR2 (chemotaxis, angiogenesis) and P2X7 (inflammasome modulation), and activates dendritic cells — the double-edged feature behind both its anti-tumor immunity and its autoimmune risk.

3. Wound Healing & Angiogenesis

LL-37 promotes keratinocyte migration and drives angiogenesis through FPRL1, stimulating VEGF, TGF-β, and bFGF expression (via a VEGFA–PI3K/AKT/mTOR axis). This is the basis for its use in chronic wounds, infected burns, and diabetic ulcers — and, in the gut, for supporting mucosal repair alongside its antimicrobial action.

The Vitamin D–LL-37 Axis (the Rate-Limiting Step)

LL-37 cannot be discussed without vitamin D. TLR activation up-regulates the vitamin D receptor (VDR) and CYP27B1 in macrophages; $1,25(OH)_2D_3$ then binds VDR and induces hCAP18/LL-37 transcription. Wound injury similarly raises CYP27B1 via TGF-β1, activating local vitamin D and LL-37. The clinical implication is direct: vitamin D status determines how much LL-37 the body can make and use — individuals with low 25(OH)D show reduced cathelicidin induction — so vitamin D optimization is both a prerequisite for exogenous LL-37 and a lever to raise endogenous LL-37 on its own.

Context-Dependent Cancer Effects

LL-37's engagement of dendritic cells and proliferation/angiogenesis pathways cuts both ways in cancer. It can be anti-tumor — binding tumor self-DNA, activating plasmacytoid dendritic cells and type-I interferon to drive T-cell immunity, with caspase-independent apoptosis (via AIF/EndoG) reported in colon, gastric, glioblastoma, and oral SCC. But it can be pro-tumorigenic in lung, breast, and ovarian cancer (via Wnt/β-catenin and NF-κB). The cancer type determines the effect — a key safety consideration.

> **Key mechanistic point: LL-37 is a vitamin-D-dependent, pleiotropic cathelicidin. It kills microbes (and disrupts biofilm far below MIC) by membrane pore formation, neutralizes LPS to calm TLR4-driven inflammation, modulates immune cells (NETs, dendritic cells, inflammasome), and promotes wound healing/angiogenesis (FPRL1, VEGF). Its dendritic-cell activation is anti-tumor in some cancers but pro-tumorigenic in others, and drives autoimmune flares in psoriasis/lupus. Without adequate vitamin D, it barely works.**

SECTION 3 · POINTS OF CLINICAL RELEVANCE

1. **A natural fit for gut health.** It is the gut's own antimicrobial — and that is the recovery/gut rationale.

Cathelicidins are produced mainly in the large bowel, where LL-37 is the principal natural antimicrobial. In the gut-stabilization context, it targets dysbiosis, biofilm-associated and drug-resistant infection, SIBO with candida, and H. pylori, while its LPS-neutralizing, immunomodulatory arm restrains the inflammation that accompanies barrier breakdown. It addresses the infection/immune side of gut dysfunction that barrier and repair peptides do not.

2. **No vitamin D, no LL-37.** Vitamin D status is the master switch — fix it first.

Because vitamin D drives LL-37 transcription, the peptide is largely ineffective when vitamin D is low. The practical rule is to optimize vitamin D before (and during) any LL-37 use — targeting roughly 60–80 ng/mL of 25(OH)D for optimal cathelicidin expression. Often, simply correcting vitamin D raises endogenous LL-37 enough to help, especially in the gut, and is a reasonable first step on its own.

3. **Sub-MIC biofilm disruption.** Its anti-biofilm power shows up at tiny concentrations.

LL-37 disrupts biofilms at concentrations far below those needed to kill the organism outright (e.g., ~128× below MIC for P. aeruginosa). Since biofilm is central to chronic and recurrent infections — including in the gut and in chronic wounds — this low-dose anti-biofilm effect, plus synergy with conventional antibiotics and very low resistance development, is one of its most useful features.

4. **Helpful in some cancers, harmful in others.** The cancer effect is context-dependent — know the exceptions.

LL-37 can mount anti-tumor immunity in cancers like colon, gastric, glioblastoma, and oral SCC, but it is pro-tumorigenic in lung, breast, and ovarian cancer. A cancer history therefore demands careful review before use, and active non-melanoma malignancy is a red flag.

5. **Avoid in psoriasis and lupus.** Autoimmune disease is a hard boundary.

LL-37 activates plasmacytoid dendritic cells and the NLRP3 inflammasome, and in psoriasis and lupus it is already elevated and central to the pathology. Giving more LL-37 in these conditions can worsen the autoimmune process, so they are contraindications; immunocompromised states and concurrent immunotherapy also warrant caution.

6. **Mind the evidence base.** Human data is limited — most evidence is preclinical.

Apart from a Phase I intratumoral melanoma trial, the efficacy data is in-vitro and animal (antimicrobial, anti-biofilm, sepsis, wound healing). LL-37 is also proteolytically unstable and expensive to manufacture authentically — reasons that analogs/fragments (GF-17, KR-12, FF/CAP18) and nanoparticle delivery are being developed. Use should be time-limited and monitored.

SECTION 4 · DOSING, DELIVERY, AND MONITORING

> **LL-37 is not FDA-approved and has no validated human dosing outside a Phase I melanoma trial. The ranges below reflect clinical practice and preclinical work. STEP ONE is always to optimize vitamin D (target ~60–80 ng/mL) — LL-37 is largely ineffective without it.**

Practitioner Dosing (Clinical Convention)

Use	Dose	Duration
General / infection (SC)	100–500 mcg (usually ~200 mcg), once or twice daily	~6 weeks, then reassess
GI / immunomodulatory (SC)	Lower end, ~200 mcg/day	Up to 12 weeks
Short-term high dose	Up to ~1 g/day	5–7 days maximum
Wound / site-specific	100–250 mcg at the wound site, twice daily	Until closure (~7–14 days)

Route is typically subcutaneous. Courses generally run ~6 weeks for infection and up to 12 weeks for GI/immunomodulatory use — not longer than 8–12 weeks before a break — then cycled. Tailor to the target (UTI, respiratory or other infection, SIBO/candida, H. pylori, GI immunomodulation).

Reference Concentrations (Preclinical)

- Antimicrobial MIC ~1–64 µg/mL; anti-biofilm ~0.5 µg/mL (well below MIC); sepsis 1 mg/kg IV (rat); eukaryotic cytotoxicity threshold ~13–25 µM — the upper bound to respect.

Vitamin D Optimization (Do This First)

1. Assess baseline 25(OH)D.
2. Target ~60–80 ng/mL for optimal cathelicidin expression.
3. Supplement with vitamin D3 (cholecalciferol) as needed; recheck at 8–12 weeks.
4. Consider vitamin D optimization alone as an initial strategy — it raises endogenous LL-37.

Monitoring

- 25(OH)D (status governs LL-37 activity); CBC with differential.
- Inflammatory markers (CRP, ESR, IL-6, TNF-α); liver and renal panels.
- Injection-site reactions (Grade 3 skin reactions noted in trial); watch for signs of autoimmune/excessive inflammatory activation.
- Track the targeted outcome (e.g., GI symptoms, wound closure) and document dose, route, duration, and cycling.

SECTION 5 · EVIDENCE PROFILE

Antimicrobial & Anti-Biofilm (In Vitro)

- Broad-spectrum killing (Gram-positive, Gram-negative, fungi, viruses), including drug-resistant isolates; kills intracellular S. aureus in macrophages at ~2 µg/mL.
- Disrupts P. aeruginosa biofilm at 0.5 µg/mL — ~128× below MIC; synergy with conventional antibiotics (e.g., daptomycin).

Sepsis & Anti-Inflammatory (Animal)

- 1 mg/kg IV reduced lethality across three rat sepsis models and lowered endotoxin and TNF-α comparably to polymyxin B; suppressed macrophage pyroptosis (CLP model).
- Most effective sepsis combination in animal work: LL-37 + imipenem.

Wound Healing & Cancer

- **Wound healing (in vitro/animal):** promotes keratinocyte migration and angiogenesis (FPRL1; VEGF/TGF-β/bFGF) — basis for chronic wound, burn, and diabetic-ulcer use.
- **Cancer (Phase I + mechanistic):** Phase I intratumoral trial in melanoma (NCT02225366); anti-tumor in colon/gastric/glioblastoma/oral SCC, but pro-tumorigenic in lung/breast/ovarian.

Evidence-Tier Summary

Claim	Evidence Tier
Broad-spectrum antimicrobial; sub-MIC anti-biofilm	In vitro (strong, consistent)
LPS neutralization / sepsis mortality reduction	Animal
Wound healing / angiogenesis	In vitro / animal
Vitamin D regulates LL-37 expression	Clinical / mechanistic

Claim	Evidence Tier
Context-dependent cancer effects	Phase I (melanoma) + review/mechanistic
Human efficacy for gut/recovery indications	Limited — largely preclinical extrapolation

Limitations

- Human clinical data is limited (one Phase I melanoma trial); optimal dosing and routes for gut/recovery use are undefined.
- Proteolytic instability, dose-dependent cytotoxicity (>~13–25 μM), high manufacturing cost; authentic product matters.
- Context-dependent cancer effects and autoimmune exacerbation potential require careful patient selection.

SECTION 6 · CLINICAL CONSIDERATIONS

Contraindications (Red Flags)

- Autoimmune disease — especially psoriasis (LL-37-DNA complexes activate pDCs) and lupus (NET–LL-37–NLRP3 inflammasome activation); LL-37 is already elevated in these conditions.
- Active malignancy — particularly non-melanoma cancers known to be promoted (lung, breast, ovarian).
- Pregnancy and lactation (no safety data); immunocompromised states (unpredictable immunomodulation).

Precautions

- Use caution with concurrent immunotherapy; monitor for excessive inflammatory responses.
- Respect the cytotoxic threshold (~13–25 μM); injection-site reactions can occur.
- Confirm authentic LL-37 — it is expensive and proteolytically unstable, so product quality is a real concern.

Safety Snapshot

Parameter	Finding
Eukaryotic cytotoxicity	Dose-dependent; ~13–25 μM threshold
Rat sepsis (1 mg/kg IV)	Well-tolerated; reduced mortality
Phase I melanoma	Grade 3 injection-site reactions possible
Resistance development	Very low
Autoimmune	Can exacerbate psoriasis / lupus

Patient Selection & Posture

The most reasonable uses are chronic or biofilm-associated and drug-resistant infections, gut dysbiosis/SIBO (with candida or H. pylori contexts), and chronic wounds — in patients without autoimmune disease or a concerning cancer history, and after vitamin D has been optimized. Pre-treatment assessment should include baseline 25(OH)D, autoimmune screening, a cancer-history review, and baseline inflammatory markers. Keep courses time-limited (generally ≤8–12 weeks, cycled), use verified product with informed consent about the investigational status and the cancer/autoimmune cautions, and document outcomes — including LL-37 levels where available — to build the evidence base.

SECTION 7 · A FINAL NOTE

LL-37 is the body's only cathelicidin and one of its most versatile defense molecules — and in the recovery and gut-stabilization context, that versatility is exactly the point. The gut is where cathelicidins are chiefly made, and LL-37 is its native antimicrobial: it kills a broad range of bacteria, fungi, and viruses, dismantles biofilms at concentrations far below those needed to kill outright, neutralizes the LPS endotoxin that drives inflammation when the barrier leaks, and supports mucosal and wound repair through angiogenesis and growth-factor signaling. For dysbiosis, biofilm-associated or resistant infection, SIBO with candida, and H. pylori-related problems, it addresses the infection-and-immune side of gut dysfunction that barrier and repair peptides leave untouched.

Two truths must travel with that promise. First, LL-37 is vitamin-D-dependent in the most literal sense — vitamin D drives its transcription, so without an optimized vitamin D status (roughly 60–80 ng/mL) the peptide barely works; correcting vitamin D is both the prerequisite and, frequently, a meaningful therapy in itself. Second, LL-37's power to activate immune cells is double-edged: it can mount anti-tumor immunity in some cancers yet promote others (lung, breast, ovarian), and it can inflame autoimmune disease — psoriasis and lupus, where it is already elevated, are firm contraindications. The same molecule that protects the gut can, in the wrong host, do harm.

For the practitioner, the posture is one of respect and precision. Optimize vitamin D first. Screen for autoimmune disease and cancer history. Use authentic product at measured doses — commonly subcutaneous around 200 mcg once or twice daily, with short high-dose bursts (up to ~1 g/day for 5–7 days) or site-specific wound dosing where appropriate — in time-limited courses (generally 6 weeks for infection, up to 12 for GI/immunomodulation), cycled rather than continuous. Monitor vitamin D, inflammatory markers, and the clinical target, and document carefully. Used within those guardrails, LL-37 is a genuinely exciting, broadly capable peptide for gut and tissue defense — powerful precisely because it does so much, and safe only when its context is respected.

> **Bottom line: LL-37 is the only human cathelicidin — a vitamin-D-dependent, pleiotropic antimicrobial peptide made chiefly in the gut. It kills broadly (and disrupts biofilm far below MIC), neutralizes LPS to calm TLR4-driven inflammation, modulates immune cells, and supports wound healing/angiogenesis — a strong fit for dysbiosis, biofilm/resistant infection, SIBO+candida, H. pylori, and chronic wounds. Optimize vitamin D FIRST (target ~60–80 ng/mL) or it won't work. Practitioner dosing is SC ~100–500 mcg (usually ~200 mcg) 1–2×/day, ~6-week courses (up to 12 for GI), cycled; up to ~1 g/day for 5–7 days short-term; 100–250 mcg twice daily at wound sites. Hard cautions: context-dependent cancer effects (avoid in lung/breast/ovarian and active non-melanoma malignancy) and autoimmune exacerbation (avoid in psoriasis and lupus). Not FDA-approved; human data limited.**

Selected References

1. Nijnik A, Hancock REW. The roles of cathelicidin LL-37 in immune defences and novel clinical applications. Curr Opin Hematol. 2009;16(1):41–47.
2. Duplantier AJ, van Hoek ML. The human cathelicidin antimicrobial peptide LL-37 as a potential treatment for polymicrobial infected wounds. Front Immunol. 2013;4:143.
3. Kahlenberg JM, Carmona-Rivera C, Smith CK, Kaplan MJ. Neutrophil extracellular trap-associated protein activation of the NLRP3 inflammasome is enhanced in lupus. J Immunol. 2013;190(3):1217–1226.
4. 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.
5. 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.
6. Overhage J, Campisano A, Bains M, et al. Human host defense peptide LL-37 prevents bacterial biofilm formation. Infect Immun. 2008;76(9):4176–4182.
7. Liu PT, Stenger S, Li H, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science. 2006;311(5768):1770–1773.
8. Noore J, Noore A, Li B. Cationic antimicrobial peptide LL-37 is effective against both extra- and intracellular S. aureus. Antimicrob Agents Chemother. 2013;57(3):1283–1290.
9. Nagaoka I, Tamura H, Reich J. Therapeutic potential of cathelicidin peptide LL-37 in sepsis/ARDS. Int J Mol Sci. 2020;21(17):5973.
10. Lu F, Zhu Y, Zhang G, Liu Z. Repurposing of the antimicrobial peptide LL-37 for cancer therapy. Front Pharmacol. 2022;13:944147.
11. Memariani H, Memariani M. Antibiofilm properties of cathelicidin LL-37. World J Microbiol Biotechnol. 2023;39(4):99.
12. Sancho-Vaello E, Gil-Carton D, François P, et al. The structure of the antimicrobial human cathelicidin LL-37 shows oligomerization and channel formation. Sci Rep. 2020;10(1):17356.
13. Tangpricha V, Judd SE, et al. LL-37 concentrations and the relationship to vitamin D in HIV. AIDS Res Hum Retroviruses. 2014;30(7):670–676.
14. He Y, et al. Cathelicidin LL-37 in periodontitis: mechanisms and biomarker potential. Int Immunopharmacol. 2025;150:114277.