Antimicrobial peptides: ancient molecules with transformative health potential

Antimicrobial peptides (AMPs) represent one of nature's oldest and most versatile defense systems — and they may hold the key to solving the antibiotic resistance crisis. These small, positively charged proteins, found in virtually every living organism from bacteria to humans, do far more than kill microbes. PubMed Central They fight viruses, destroy cancer cells, heal wounds, tame inflammation, and orchestrate immune responses. With antimicrobial resistance now killing nearly **5 million people annually** — a toll projected to double by 2050 Frontiers PubMed Central — AMPs have surged to the forefront of therapeutic research. A wave of AI-powered discovery tools has identified nearly **one million novel candidate peptides** Cell Press in just the past two years, Springer while clinical trials are testing AMP-based drugs against everything from diabetic foot ulcers to metastatic melanoma. Perhaps most remarkably, the human body's own production of these peptides is directly regulated by vitamin D, offering a tangible link between nutritional status and immune defense. PubMed

What AMPs are and how they wage war on pathogens

Antimicrobial peptides are small bioactive molecules, typically **10–50 amino acids long**, ASM Journals carrying a net positive charge (+2 to +9) and an amphipathic structure — one face hydrophobic, the other hydrophilic. Springer This molecular architecture is the foundation of their killing power. The Antimicrobial Peptide Database (APD3) catalogs roughly 3,940 peptides from six kingdoms of life, while the broader DBAASP database lists approximately 18,400. Springer Springer

In humans, three major AMP families dominate innate defense. **Defensins** split into α-defensins (like HNP-1 through HNP-4 in neutrophils, where they constitute up to 50% of total protein, Exploration Publishing and HD-5/HD-6 in intestinal Paneth cells) and β-defensins (hBD-1 through hBD-4, expressed broadly across epithelial surfaces). **Cathelicidins** are represented by a single gene in humans — CAMP — which encodes LL-37, a 37-amino-acid peptide Springer with an extraordinary range of functions. Wikipedia PubMed Central **Histatins**, histidine-rich peptides found in saliva, specialize in antifungal defense. Beyond humans, the AMP universe includes magainins MDPI from frog skin, cecropins Springer from moth hemolymph, melittin from bee venom, cyclotides from plants, and nisin from bacteria ASM Journals — each shaped by millions of years of evolutionary arms races.

AMPs kill through mechanisms fundamentally different from conventional antibiotics. Rather than targeting a single enzyme or pathway, they attack microbial membranes through multiple simultaneous models. ScienceDirect In the **barrel-stave model**, peptides insert perpendicularly into the lipid bilayer to form channel-like pores. The **toroidal-pore model** involves peptides bending the lipid monolayer so that both peptides and lipid

headgroups line the pore. PubMed Central The **carpet model** sees peptides accumulating on the membrane surface until a critical threshold triggers detergent-like disintegration. PubMed Central Frontiers Many AMPs also penetrate cells to inhibit DNA, RNA, or protein synthesis PubMed Central — buforin II binds intracellular nucleic acids, while proline-rich peptides Frontiers like oncocin stall bacterial ribosomes. The recently characterized peptide plectasin binds lipid II, a cell-wall precursor, through a calcium-sensitive supramolecular mechanism. This multi-target assault is precisely why **bacteria develop resistance to AMPs far more slowly** than to conventional antibiotics: ResearchGate restructuring an entire membrane is vastly harder than mutating a single drug target. The defensin-like peptide P9R showed no resistance emergence after 40 passages in influenza virus, while the approved drug zanamivir became ineffective after just 10. News-Medical

Fighting bacteria, viruses, and fungi on multiple fronts

The antibacterial potency of AMPs extends to the most dangerous drug-resistant pathogens. The engineered peptide LI14 achieves minimum inhibitory concentrations (MICs) of 1–64 μg/mL against MRSA, VRE, carbapenem-resistant Enterobacteriaceae, and MCR-positive *E. coli* — and known resistance genes have no effect on its activity. Nature Melittin from bee venom kills MRSA at concentrations as low as **0.625 μg/mL**. Frontiers The AI-designed peptide A24 hits clinical MRSA isolates at 2–16 μg/mL with less than 3% hemolysis. Nature Sub-MIC AMP treatment can even re-sensitize vancomycin-resistant *S. aureus* to vancomycin by depolarizing bacterial membranes, PubMed Central suggesting powerful synergistic potential with existing antibiotics.

Against viruses, AMPs deploy a distinct toolkit. They disrupt viral envelopes, block receptor binding, inhibit endosomal acidification, and prevent viral fusion. Springer **Enfuvirtide (T-20)**, targeting HIV's gp41 protein, became the first FDA-approved antiviral peptide. News-Medical The broad-spectrum peptide P9R inhibits influenza (H1N1, H7N9), SARS-CoV-2, MERS-CoV, and SARS-CoV by preventing endosomal pH changes required for viral uncoating. PubMed Central Nature Urumin, isolated from South Indian frog skin, specifically targets H1 hemagglutinin and kills drug-resistant influenza strains. Human intestinal defensin HD5 acts as a natural lectin that blocks SARS-CoV-2 receptor binding, while brilacidin, a synthetic defensin-mimetic, inhibits the virus synergistically with remdesivir. SEC.gov News-Medical

Antifungal activity rounds out the antimicrobial trifecta. With the WHO designating 19 fungal species as priority pathogens and only four classes of conventional antifungals available, AMPs offer critical alternatives. PubMed Central Histatin 5 from human saliva is active against amphotericin B-resistant *Candida albicans* and fluconazole-resistant *C. glabrata*. PubMed LL-37 inhibits growth across *Candida*, *Aspergillus*, *Fusarium*, and *Trichophyton* species through cell wall disruption, membrane permeabilization, and induction of autophagy-like cell death. Frontiers Melittin combines β-glucan synthase inhibition with ROS-induced apoptosis. Frontiers These peptides kill fungi rapidly, through

diverse mechanisms, with low propensity for resistance — exactly the profile needed against emerging threats like *Candida auris*. Springer

Beyond killing: how AMPs heal wounds, fight cancer, and orchestrate immunity

The designation "host defense peptides" reflects a crucial insight: **the primary in vivo role of many AMPs is immunomodulation, not direct microbial killing**. ASM Journals Many AMPs lose antimicrobial activity at physiological salt concentrations, yet their immunomodulatory functions persist — suggesting evolution optimized them as immune signals, not just antibiotics. Frontiers

LL-37 exemplifies this dual identity. In sepsis, it directly binds and neutralizes bacterial lipopolysaccharide (LPS), blocking TLR4 activation and suppressing NF-κB signaling. PubMed Central Revolution Health In rat sepsis models, LL-37 at 1 mg/kg intravenously reduced lethality comparably to imipenem while achieving lower endotoxin and TNF-α levels than conventional antibiotics. PubMed ASM Journals It suppresses macrophage pyroptosis, enhances antimicrobial neutrophil extracellular trap release, and stimulates ectosome secretion with heightened bactericidal capacity. PubMed Defensins and LL-37 are chemotactic for neutrophils, monocytes, T cells, and immature dendritic cells MDPI — physically recruiting the immune system's full arsenal to sites of infection. PubMed Central PubMed Central By forming complexes with self-DNA and delivering it to endosomal TLR9, LL-37 bridges innate and adaptive immunity, triggering dendritic cell maturation and downstream T-cell activation. PubMed Central

In wound healing, LL-37's absence is as telling as its presence. Chronic ulcer epithelium **lacks LL-37 entirely**, while normally healing wounds express it abundantly. The peptide promotes angiogenesis by activating EGFR/ERK and PI3K/AKT/mTOR signaling in endothelial cells, drives keratinocyte migration through EGFR transactivation, Frontiers and recruits mesenchymal stem cells. PLGA nanoparticles loaded with LL-37 achieved approximately 90% wound closure by day 10 in full-thickness excisional models, significantly outperforming controls. PubMed Central AMP-loaded wound dressings — incorporating hBD-2 in collagen-chitosan scaffolds for diabetic wounds, ScienceDirect or LL-37-conjugated gold nanoparticles Preprints.org — represent an active translational frontier.

The anticancer potential of AMPs exploits a fundamental membrane difference. Cancer cells aberrantly expose phosphatidylserine on their outer membrane leaflet, PubMed Central creating a **3–7 times more negatively charged surface** than normal cells — making them electromagnetically attractive to cationic AMPs. LTX-315, a 9-mer synthetic peptide derived from bovine lactoferricin, has ACS Publications completed Phase I clinical trials demonstrating safety and de novo T-cell responses. It is now being combined with immune checkpoint inhibitors (ipilimumab, pembrolizumab) in Phase I/IIa trials for melanoma and metastatic breast cancer. LTX-315 works by triggering immunogenic cell death:

intratumoral injection causes tumor necrosis, release of damage-associated molecular patterns, dendritic cell maturation, and — remarkably — regression of untreated distant tumors (the abscopal effect). It reprograms the tumor microenvironment by decreasing regulatory T cells and myeloid-derived suppressor cells while expanding polyfunctional Th1 cytotoxic cells.

The vitamin D–cathelicidin axis links sunlight to immune defense

One of the most consequential discoveries in AMP biology is the direct molecular link between vitamin D and cathelicidin production. The landmark 2006 study by Liu et al. in *Science* demonstrated that when monocytes recognize *Mycobacterium tuberculosis* through TLR2/1, they upregulate both the vitamin D receptor (VDR) and CYP27B1 (the enzyme converting circulating 25(OH)D to active calcitriol). Calcitriol then binds PubMed Central a **vitamin D response element (VDRE)** in the CAMP gene promoter, directly activating transcription of LL-37 Oxford Academic and β-defensin 2. This pathway is unique to humans and non-human primates ScienceDaily — mice lack the functional VDRE, which is why murine models frequently miss this critical biology. PubMed Central

The clinical implications are stark. Among patients with active tuberculosis, **86% have vitamin D insufficiency** (serum 25(OH)D below 30 ng/mL), ScienceDirect and those with deficiency show significantly reduced LL-37 levels in granulomatous lesions. PubMed *M. tuberculosis* has evolved to actively downregulate LL-37 expression and autophagy genes in macrophages as an immune evasion strategy Immunenetwork — high vitamin D concentrations (1 μM) are required to restore LL-37 in infected macrophages under hyperglycemic conditions, explaining the heightened TB susceptibility in diabetic patients. PubMed Central

The connection extends well beyond tuberculosis. A 2024 randomized controlled trial found that vitamin D insufficiency (below 50 nmol/L) was associated with a **2.1-fold increased risk of acute respiratory infection** and inversely correlated with cathelicidin concentration. PubMed In a 16-week winter study of 225 endurance athletes, plasma cathelicidin positively correlated with plasma 25(OH)D, and athletes with vitamin D deficiency experienced significantly higher upper respiratory tract infection incidence, symptom days, and severity. PubMed Seasonal influenza peaks in winter precisely when 25(OH)D concentrations are lowest PubMed Central — a pattern the vitamin D–cathelicidin axis may partly explain. The combination of 4-phenylbutyrate with calcitriol can overcome pathogen-induced suppression of LL-37, representing a promising host-directed therapy strategy for MDR-TB. Taylor & Francis Online

Paradoxically, LL-37 overexpression drives pathology in certain conditions. In **psoriasis**, LL-37 complexes with self-DNA to activate plasmacytoid dendritic cells via TLR9, triggering the type I interferon cascade central to disease pathogenesis. PubMed PubMed Central LL-37 has been identified as a T-cell autoantigen in psoriasis, with serum

levels significantly elevated in affected patients. JCI In **rosacea**, disturbed cathelicidin processing PubMed by aberrant serine proteases (KLK5/KLK7) generates inflammatory LL-37 fragments that activate the NLRP3 inflammasome in mast cells. ResearchGate These dual roles — protective against infection, pathogenic in autoimmunity — highlight the exquisite context-dependency of AMP biology. Immunenetwork

Clinical pipeline and the AI revolution in AMP discovery

As of late 2024, **fewer than 30 AMPs** have received FDA or EMA approval, ASM Journals including polymyxins, daptomycin, vancomycin, gramicidin, and nisin. ASM Journals The clinical pipeline has seen both promise and setbacks. Pexiganan (a magainin analog) failed Phase III trials for diabetic foot ulcers, PubMed Central showing no superiority over standard care. ScienceDirect PubMed Central Murepavadin, a first-in-class outer membrane protein targeting antibiotic, Springer had its Phase III trial for ventilator-associated pneumonia suspended due to nephrotoxicity. MDPI Stability, toxicity, cost, and bioavailability remain the central challenges — most AMPs are susceptible to proteolytic degradation in vivo, PubMed Central lose activity in serum, and require concentrations orders of magnitude above physiological levels for direct bacterial killing. MDPI +2

The most encouraging clinical advances include brilacidin, a synthetic defensin-mimetic that met primary and secondary endpoints in Phase II for oral mucositis and showed positive results in ulcerative proctitis, SEC.gov PubMed Central and LTX-109, a peptidomimetic that effectively eradicated persistent MRSA/MSSA nasal colonization in Phase II without adverse effects. PubMed Central Strategies to overcome AMP limitations — D-amino acid incorporation, cyclization, PEGylation, lipidation, nanoparticle encapsulation, and peptidomimetic scaffolds — are steadily advancing. PubMed Central +2

The true game-changer, however, is artificial intelligence. In 2024, the AMPSphere project applied machine learning to over 63,000 metagenomes and identified **863,498 non-redundant candidate AMPs** ACS Publications Springer — of 100 synthesized, 79 were active, with 63 showing potency against critical ESKAPEE pathogens at 1–4 μmol/L. Cell Press The APEX deep-learning platform mined proteomes of extinct organisms, discovering peptides from woolly mammoths ("mammuthusin") and ancient elephants ("elephasin") with preclinical antibacterial activity. ACS Publications In 2025, the ProteoGPT generative AI pipeline screened hundreds of millions of sequences to yield AMPs effective against ICU-derived carbapenem-resistant *Acinetobacter baumannii* with reduced resistance susceptibility. Nature Springer These AI tools are compressing discovery timelines from decades to months, transforming AMPs from academic curiosities into a scalable therapeutic platform. Nature

Conclusion

Antimicrobial peptides sit at a unique intersection of evolutionary biology, immunology,

and drug discovery. Their multi-target mechanisms make resistance development inherently difficult — a decisive advantage over conventional antibiotics as resistance accelerates globally. Frontiers ScienceDirect The vitamin D–cathelicidin axis reveals that something as simple as correcting vitamin D deficiency can measurably enhance innate antimicrobial defense, with direct implications for tuberculosis, respiratory infections, and potentially pandemic preparedness. The immunomodulatory and anticancer properties of peptides like LL-37 Immunenetwork +2 and LTX-315 extend AMP relevance far beyond infectious disease into oncology, wound care, and autoimmune conditions. PubMed Central PubMed Central While clinical translation has been slowed by stability and toxicity challenges, AI-driven discovery is now generating candidates at unprecedented scale PubMed Central PubMed Central — nearly a million in a single study — while nanoparticle delivery and peptidomimetic design are systematically addressing pharmacological limitations. Science +2 The field is no longer asking whether AMPs can become therapeutics, but how fast they can be brought to patients who need them.