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### Chemical Modifications of Antimicrobial Peptides: Database, Classification and New Opportunities

#### Introduction

Host defense antimicrobial peptides (AMPs) are natural products isolated from six life kingdoms: bacteria, archaea, protists, fungi, plants, and animals.<sup>1</sup> They play a critical role in protecting the host from infection. Because of their efficacy against antibiotic-resistant pathogens, including biofilms, AMPs constitute important candidates for developing a new generation of antimicrobials.

#### Methods

To promote antimicrobial development, it is useful to put information in order in a database. My group created the antimicrobial peptide database (APD) in 2004.<sup>2</sup> The APD was constructed based on the LAMP software bundle, including Red Hat Linux operating system using the freeware Apache web server, MySQL relational database management system, and PHP script language. In 2021, this database was reprogrammed to enhance cybersecurity. The APD is accessible currently at <https://aps.unmc.edu>.

#### Results

Information scope in the APD has been expanding for 20 years.<sup>2</sup> The first version of the APD with 525 entries annotated antibacterial, antiviral, antifungal, hemolytic, and anticancer activities. The second version APD2 with 1228 peptides added anti-HIV, Anti-Gram+, anti-Gram-, and anti-LPS peptides. Additional peptide activities (e.g., antiparasitic, spermicidal, insecticidal, chemotactic, wound healing, antioxidant, protease inhibitor, and antibiofilm) were included in the APD3 (with 2619 AMPs), leading to a total of 19 types.<sup>1</sup> Meanwhile, post-translational modifications and peptide binding targets have also been expanded. The APD has now entered a new phase by including natural, synthetic, and AI predicted peptides.<sup>4</sup> This database is now most comprehensive by registering a variety of information for antimicrobial development, ranging from peptide discovery, mechanisms of action, stability and production, to potential applications of these peptides in agriculture, food industry, and clinical care.

#### Discussion

Classically, AMPs were discovered by following the isolation, purification, and characterization procedure. With the available of the APD that comprise AMPs with known activity, it is now fashionable to discover AMPs via AI prediction. AI discovery is in fact a knowledge-based method. It covers a wide range of methods from the initial de novo design to the current multilayers to mimic human neural networks. Sequence alignment-based methods were found to be highly accurate. Newly developed computing tools enable genome mining of novel antimicrobial gene clusters, accelerating antibiotic discovery. Chemical modification diversifies the structural scaffolds of natural AMPs and provides a basis for universal peptide classification.<sup>3</sup> In laboratories, chemical modifications play a central role in improving peptide properties for different applications.<sup>4</sup> A major goal of chemical modification is to achieve the desired stability to proteases from both the host and pathogens. Finally, an engineered peptide is anticipated to possess potency, selectivity, and stability for potential medical use.

#### References

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