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Poster abstract submission

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Presenting author Liz Armas Egas

Presenting author's email liz.armas@bsse.ethz.ch

Further authors (if any)
Sven Panke, Martin Held

Affiliation(s)
D-BSSE, ETH Zurich

Country Switzerland

Type of organization Academic / research institution

Poster title
Chimerophore antibiotics: Engineering intramolecular synergy to tackle antimicrobial resistance

Poster abstract

The rise of multi-drug-resistant pathogens underscores the need for new antibiotics. Host defense peptides (HDPs) such as oncocin and apidaecin, offer a promising avenue due to their ability to penetrate Gram-negative bacterial membranes and target intracellular sites. These proline-rich HDPs (PrHDPs) adopt secondary structures (polyproline type II-helices) that confer recalcitrance to proteolytic degradation and enable non-mebranolytic mechanisms of action and selective binding to bacterial targets. However, optimizing these peptides for clinical application requires further enhancing their stability and minimizing the potential for resistance development.

To address these challenges, we designed a library of 97,235 chimerophores by pairing the pharmacophores of 56 distinct parent HDPs via short amino acid linkers. This strategy aimed to create peptides that target two independent intracellular sites and utilize different cellular entry pathways, thereby significantly reducing the likelihood of resistance-attributing mutations. Next-generation sequencing (NGS)-supported Mex screening (Koch et al., 2021) in recombinant Escherichia coli identified over 30,000 intracellularly active chimerophores, confirming the success of the combinatorial approach. A focused set of 18 chemically synthesized chimerophores, derived from the Mex-positive fraction, demonstrated potent activity against a broad range of Gram-negative bacteria, including WHO-priority pathogens Pseudomonas aeruginosa, Acinetobacter baumannii, and Klebsiella pneumoniae. Notably, chimerophores expanded the spectrum of their parents, showing efficacy against Gram-positive bacteria, such as clinical isolates of Staphylococcus aureus. Single-cell analysis confirmed that chimerophores inherit the non-membranolytic mechanism from their parents. Moreover, in vitro assays demonstrated that chimerophores maintain both parental targets, resulting in an intramolecular synergistic effect that yields a superior antimicrobial strategy. This synergistic nature of chimerophores enabled high potency, low cytotoxicity, high therapeutic indices, improved serum stability and a robust defense against resistance emergence in P. aeruginosa in a 21-day serial passage assay.

Our findings highlight the potential of chimerophores as multitargeting antimicrobial agents that can overcome resistance mechanisms, expand the spectrum of bacterial targets, and offer new therapeutic options against multi-drug-resistant pathogens.

Research topic

Biological therapeutics