Trainee Research Highlight

International Community for the Advancement of Peptoids — ICAP

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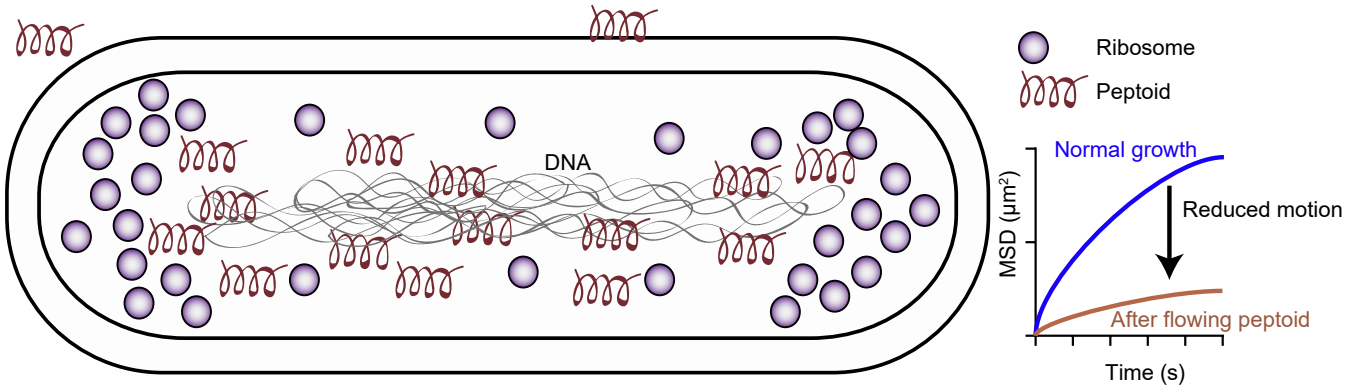
Antimicrobial peptoids pass rapidly through bacterial membranes and flocculate ribosomes and DNA

Zhu, Y., Nielsen, J. E., Molchanova, N., Mustafi, M., Herlan, C., Fleck, B., Bräse, S., Schepers, U., Sørensen, K., Zielke, C., Lin, J. S., Weisshaar, J. C., Jenssen, H., Barron, A. E., *Proc. Natl. Acad. Sci.*, **123**, e2535920123 (2026).



Active peptoids freeze cytoplasm in live *E.coli* cells

Active peptoids reduce the motion of key macromolecules, including chromosomal DNA and ribosomes in live *E. coli* cells, as demonstrated by mean squared displacement (MSD). They achieve this by creating a dense network of linkages between these intracellular polyanionic biopolymers, leading to cytoplasmic rigidification.

Scientific Achievement:

This study shows that synthetic, protease-resistant peptoids mimic natural host defense peptides such as LL-37, killing bacteria *via* membrane permeabilization and cytoplasmic rigidification. Utilizing time-resolved, live-cell fluorescence microscopy and single-particle tracking to quantify the real-time effects of a series of peptoids on *E. coli*, the study demonstrates that active peptoids rapidly penetrate the bacterial membrane and flood the cytoplasm, forming electrostatic interactions with intracellular polyanionic biopolymers (DNA, RNA, and ribosomes). This creates a dense network of pseudo-crosslinks that freezes macromolecular motion, transforming the dynamic cytoplasm into a rigid, gel-like state. Furthermore, the work elucidates the precise biophysical actions of these peptoids, classifies their antimicrobial potency based on their ability to permeabilize membranes and rigidify cytoplasm, and correlates these mechanisms with their chemical structures. This work provides a promising foundation for developing potent, broad-spectrum therapeutics that exploit both membrane disruption and macromolecular crosslinking to achieve robust bacterial killing.

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Why is this paper significant?

"This study marks an advancement in biomimetic anti-infectives by demonstrating that peptoids share the ability of natural antimicrobial peptides to permeabilize membranes and rigidify the cytoplasm of bacteria, while being invulnerable to protease degradation. Using a suite of biophysical methods, including super-resolution imaging and soft X-ray tomography, the research demonstrates that active peptoids bind and flocculate DNA and ribosomes, causing a catastrophic "freezing" of the cytoplasm. Because this mechanism induces a physical shutdown of the cell, it is resilient to common bacterial resistance pathways like single-point mutations. This work redefines the paradigm for developing next-generation anti-infectives against multi-drug-resistant pathogens."

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