Sophisticated Peptide Antibiotics

Kim Lewis

Antimicrobial Discovery Center, Northeastern University, Boston, MA USA k.lewis@neu.edu

We are experiencing an Antimicrobial Resistance Crisis, a slow-moving pandemic, according to the WHO. This calls for antibiotics that avoid resistance development, and are capable of acting against dormant persister cells responsible for recalcitrance of chronic infections, a source of resistant mutants and an unsolved problem in its own right. We are developing several peptide antibiotics with unusual modes of action that go well beyond a simple inhibition of the target, to address these challenges. Acyldepsipeptide kills persister cells by activating proteolysis (1). Teixobactin binds to precursors of peptidoglycan and wall teichoic acid (2), and forms a supramolecular structure that damages the membrane (3). Clovibactin binds to a minimal, immutable PiPi moiety of Lipid II, and forms a supramolecular structure that causes cell lysis (4). There is no detectable resistance to teixobactin and clovibactin. Darobactin (5, 6) and dynobactin (7) bind the the “undruggable” β-barrel BamA protein on the surface of Gram-negative bacteria. The binding is based on peptide backbone interactions, precluding resistance development.

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