Novel Antimicrobial Agent Development from Unprecedented Targets

Drug Discovery

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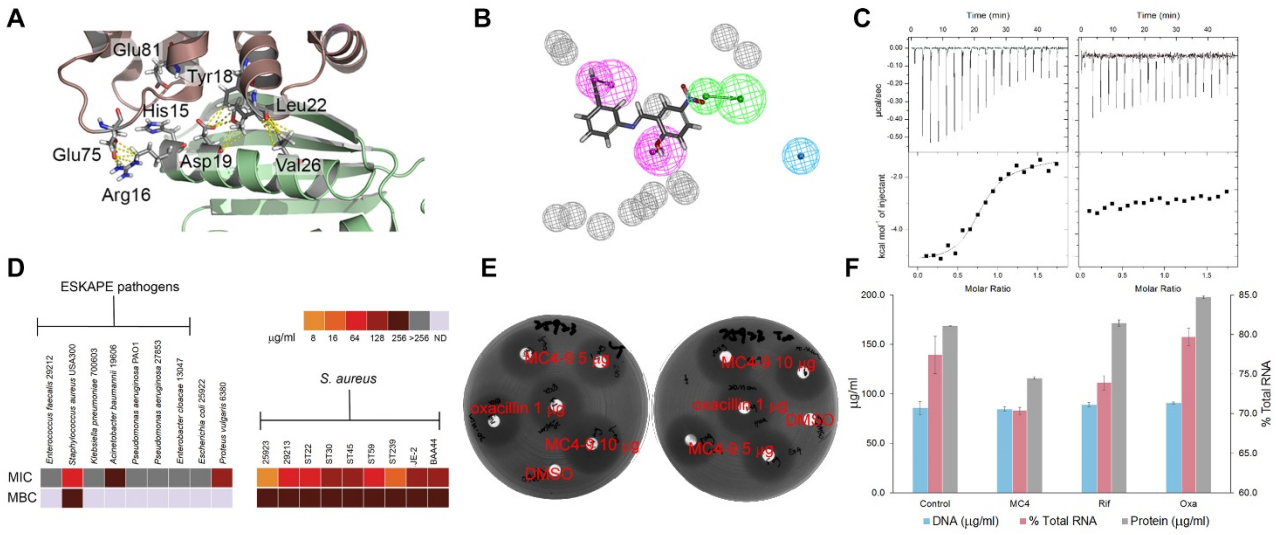
. Structure-Based Drug Design from Protein-Protein Interactions in Bacterial Transcription .

Bacterial infections are causing re-emerging epidemics invasive to human health and global economy due to antimicrobial resistance. To solve this problem, we focus on studying an underutilized drug target, bacterial transcription responsible for RNA synthesis to develop the "3N" type antimicrobial agents (New structure, New target, New mechanism). Structure-based drug design (SBDD) strategy was used for screen-to-hit identification targeting protein-protein interactions (PPIs) in bacterial transcription as unprecedented drug targets. Several hit compounds as the inhibitors of various PPIs are being optimized to show potent antibacterial activity comparable to commercially available antibiotics against clinical pathogenic species such as *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Clostridium difficile*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. The current hit-to-lead process is expected to provide potential antimicrobial drug candidates in the near future for further development.



A) NusB protein - NusE protein interaction; **B)** Hit compound **MC4** docked into pharmacophore model;
C) **MC4** interacted with NusB; **D)** Antibacterial activity of **MC4** against antibiotic-resistant *S. aureus* strains;
E) Disc diffusion assay of one derivative **MC4-9** compared to oxacillin; **F)** **MC4** inhibits rRNA synthesis in *S. aureus* cells.

Representative Publications:

1. Yang X, Luo MJ, Yeung ACM, Lewis PJ, Chan PKS, Ip M, Ma C. (2017) First-In-Class Inhibitor of Ribosomal RNA Synthesis with Antimicrobial Activity against *Staphylococcus aureus*. Biochemistry 56, 5049-5052.
2. Ma C, Yang X, Lewis PJ. (2016) Bacterial Transcription as a Target for Antibacterial Drug Development. Microbiology and Molecular Biology Reviews 80, 139-160.
3. Ma C, Yang X, Lewis PJ. (2016) Bacterial Transcription Inhibitor of RNA Polymerase Holoenzyme Formation by Structure-Based Drug Design: From in Silico Screening to Validation. ACS Infectious Diseases 2, 39-46.

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