Inhibiting heme piracy by pathogenic Escherichia coli using de novo-designed proteins

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Background: Pathogenic *E. coli* rely on heme acquisition systems, such as ChuA, to obtain iron from host hemoproteins during infection. These TonB-dependent transporters (TBDTs) enable bacteria to overcome host nutritional immunity, making them key virulence factors. Traditional antibiotics do not specifically target such nutrient uptake mechanisms, motivating new strategies that block heme piracy without affecting bacterial viability directly

Objective: This study aimed to design and evaluate artificial heme-binding proteins that can competitively inhibit heme uptake by *E. coli* ChuA

Results: The authors first confirmed that ChuA exhibits high specificity toward hemoglobin. They then employed Cryo-EM, X-ray crystallography, and AlphaFold to investigate the molecular details of this interaction. Two key amino acid residues, His-86 and His-420, were identified as essential for extracting heme from hemoglobin. To prevent bacteria from acquiring heme through ChuA, the authors used AI-based de novo protein design to create potential inhibitors, which were subsequently screened for activity. The selected inhibitors were shown to effectively suppress bacterial growth. Finally, structural comparison between the AI-designed biners and those resolved by Cryo-EM and X-ray crystallography revealed an almost perfect match, validating feasibility of the design approach.

Conclusion: This study demonstrates a novel anti-virulence approach that targets bacterial iron acquisition through de novo-designed heme-binding proteins. By preventing heme piracy rather than killing the bacteria, this strategy may reduce selective pressure for resistance development. The study highlights the potential of protein design in developing next-generation therapeutics against pathogenic *bacteria*