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Combating Antibiotic Resistance: Emerging Therapeutic Strategies Targeting Bacterial Proteins.

Stefan Larsson*

Department of Infectious Diseases, Institute of Biomedicine, University of Gothenburg, Sweden

***Correspondence to**: Stefan Larsson, Department of Infectious Diseases, Institute of Biomedicine, University of Gothenburg, Sweden, China. E-mail: s.larsson@fysiologi.gu.se

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Introduction

Antibiotic resistance (AR) is one of the most pressing global health challenges of the 21st century. The rise of multidrug-resistant (MDR) and extensively drug-resistant (XDR) bacteria has rendered many conventional antibiotics ineffective, threatening the success of modern medicine [1, 2].

Central to this crisis is the ability of bacteria to evolve and deploy mechanisms that neutralize antibiotic action—many of which involve bacterial proteins. Targeting these proteins offers a promising avenue for developing novel therapeutic strategies that can overcome resistance and restore treatment efficacy [3, 4].

Understanding these protein-based mechanisms is essential for designing targeted therapies. Advances in structural biology have enabled detailed visualization of bacterial proteins involved in resistance. Techniques such as X-ray crystallography and cryo-electron microscopy reveal active sites and conformational changes, guiding rational drug design [5, 6].

For example, inhibitors targeting the active site of NDM-1 (New Delhi metallo-β-lactamase) have shown promise in restoring β-lactam efficacy. Similarly, structural insights into MCR-1, a protein conferring colistin resistance, have led to the development of molecules that block its lipid A modification activity [7, 8].

New-generation inhibitors like avibactam and relebactam neutralize β-lactamases, restoring the activity of β-lactam antibiotics against resistant strains. Compounds that inhibit efflux pumps enhance intracellular antibiotic concentrations. Research into targeting AcrAB-TolC and NorA pumps is ongoing. Instead of killing bacteria, these therapies disarm them by targeting virulence factors such as toxins and adhesion proteins, reducing selective pressure for resistance. Bacteriophages can be engineered to deliver proteins that degrade resistance genes or disrupt biofilms [9, 10].

Conclusion

AMPs interact with bacterial membranes and proteins, offering broad-spectrum activity with low resistance potential. Nanoparticles can be functionalized to deliver antibiotics or inhibitors directly to bacterial proteins. For instance, silver nanoparticles have been shown to disrupt protein synthesis and membrane integrity in resistant bacteria. Nanocarriers can also be designed to bypass efflux pumps and release drugs in response to bacterial enzymes, enhancing specificity and reducing toxicity. Computational tools are accelerating the discovery of protein targets and inhibitors. Molecular docking, virtual screening, and machine learning models predict interactions between bacterial proteins and candidate drugs. Databases like PDB and UniProt provide structural and functional annotations, while platforms like Auto Dock and Rosetta enable simulation of drug-protein binding. Addressing these challenges requires interdisciplinary collaboration and robust clinical trials. Public awareness and education are also vital to ensure responsible antibiotic use. These innovations, combined with traditional approaches, offer hope for reversing the tide of resistance.

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