

Design and Development of Siderophore-Macrolide Antibiotic Conjugates to Combat Multidrug Resistance (MDR) Gram-Negative Bacterial Infections

Graphical Abstract/ Layout



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Name of the Funding Agency

Indian Council for Medical Research
(ICMR)

Name of the Scheme

Small Extramural Grants

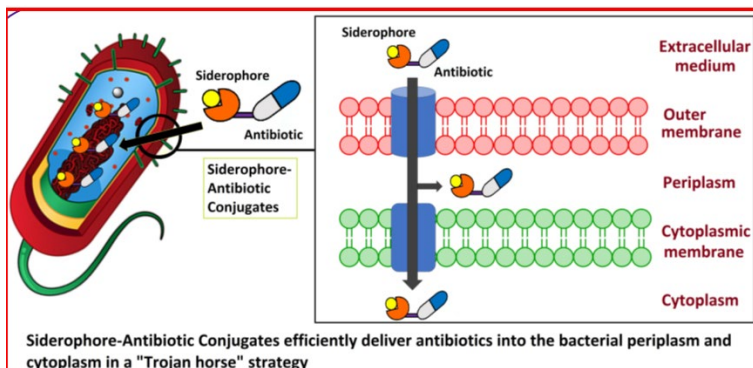
Sanctioned Amount (in Rupees)

Rs. 52,68,585

Duration of the Project (years)

3

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Project Description

Antimicrobial resistance (AMR) is an urgent and escalating global health concern, with the rise of Gram-negative bacteria that resist most antibiotics due to their double membrane barrier. This issue underscores the critical need for potent and selective antibiotic delivery strategies for these resistant bacteria. Generally, bacteria have specific outer membrane transporters that use siderophores to translocate ferric ions into the bacterial cell. Macrolides, which target bacterial ribosomes and specific enzymes, are highly susceptible to efflux but do not cross the polar Gram-negative outer membrane. Enhancing the potency of macrolide antibiotics against these bacteria remains unexplored.

Recently, the FDA approved the siderophore conjugate drug cefiderocol (Fetroja) by Shionogi & Company Ltd to treat Gram-negative urinary infections. Hence, the conjugation of Gram-positive macrolide antibiotics to siderophores provides opportunities to deliver potent antibiotics to Gram-negative bacteria using Nature's Trojan horse approach. These trojan-horse conjugates are expected to increase the membrane permeability of Gram-negative bacteria and allow the repurposing of currently available Gram-positive-only macrolide antibiotics for the treatment of drug-resistant Gram-negative bacteria.

Products/ Instruments/ Results/ Outreach Activities (Pictures)



Laboratory shaker LP360AMP
for solid-phase peptide synthesis

List of publications:

1. Lakshminarayanan K, Murugan D, Venkatesan J, Vasanthakumari Thirumalaiswamy H, Gadais C, Rangasamy L. Siderophore-Conjugated Antifungals: A Strategy to Potentially Cure Fungal Infections. *ACS Infect Dis.* 2024. (Impact Factor 4.0)
2. Venkatesan J, Murugan D, Lakshminarayanan K, Smith Alexis R Thirumalaiswamy Vasanthakumari H, Kandhasamy H, Zender B, Zheng G, Rangasamy L. Powering Up Targeted Protein Degradation Through Active and Passive Tumour-Targeting Strategies: Current and Future Scopes. *Pharmacology & Therapeutics.* 2024. (Impact Factor 12.0)