Development of a multipronged antibacterial candidate to treat drug-resistant bacterial infections

Project Lead: Prof. Venkateswarlu Yarlagadda

Specific problem being addressed: According to the recent report from the Indian Council of Medical Research (ICMR), AMR is rising in India in common pathogens that were once susceptible. Some of the concerning pathogens that are difficult to treat due to a lack of effective therapeutics are drug-resistant Staphylococci, Enterococci, Mycobacterium tuberculosis, and drug-resistant Gram-negative bacteria. Therefore, this ever-increasing AMR calls for continuous efforts for the discovery and development of durable antimicrobials with novel modes of action. Our proposal aims to develop an antimicrobial agent with multiple modes of action so that even if bacteria develop resistance to one mode, the other modes will still work and act against drug-resistant bacteria. Such multifaceted antibiotics are expected to have long-term utility in clinics.

Project Summary: To combat the clinical spread of antimicrobial resistance (AMR), new agents with novel mechanisms of action (MOA) that are not cross-resistant to existing drug classes and are not susceptible to rapid resistance selection are required. Many natural product antibiotics were discovered during the "golden age of antibiotic discovery," but most of them were overlooked due to poor pharmacological properties, for eg. Moenimycin A. The newly synthesized analogues are envisioned to demonstrate more than one antibacterial mechanism. Since there are no medications in clinical use that target cell wall pyrophosphates, the unique strategy put forward in our work includes targeting bacterial pyrophosphates. The antibacterial potency will be assessed against a range of drug-resistant Gram-positive and Gram-negative bacteria. Because of their several modes of action, the novel analogues are anticipated to have remarkable antibacterial efficacy against a range of bacterial pathogens, including those of the infectious species that pose an immediate danger. In order to incorporate the cell wall lipid targeting property as an additional mode of action and potentially create dual targeted antibiotics, we are also extending the reach of this strategy to other classes of antibiotics, including erythromycin, tetracycline, fluoroquinolone, β-lactam antibiotics, sulfonamide, and rifamycin.

Impact of this innovation: Antimicrobial resistance (AMR) has emerged as a primary threat to the treatment of infectious diseases and indeed all modern medicine. In fact, AMR is viewed as a slow-moving silent pandemic with catastrophic economic consequences, with the potential to cause 10 million deaths every year by 2050. The evolution of bacterial antibiotic resistance occurs by natural selection, which is unavoidable as AMR evolved in parallel to the antibiotic discovery. We believe this antibiotic drug discovery research provides new ways to fight against bacterial infections and can be translated into a long-term research project.