List of ten best papers of the candidate, highlighting important discoveries/contributions described in them briefly (not to exceed 3000 words)

Total Publications: 77 Research Articles (58 as corresponding author) + 9 Review articles (8 as corresponding author) + 7 Book Chapters (6 as corresponding author)

Citations: 4077, **h-index:** 39, **i-10 index:** 71 (According to Google Scholar as on 27th October, 2021)

I. Sarkar, P.; Basak, D.; Mukherjee, R.; Bandow, J. E.; **Haldar, J.***. Alkyl-Aryl-Vancomycins: Multimodal Glycopeptides with Weak Dependence on the Bacterial Metabolic State. *J. Med. Chem.* **2021**, *64*, 10185-10202.

[This article reports the development of aryl-alkyl vancomycin derivatives. These derivatives are synthesized by appending different alkyl-aryl substitutions, with quaternary charge, to the amino terminal of the vancosamine sugar. The optimized lead compound, bearing phenyl-quaternary ammonium and decyl substituents, displays potent antibacterial activity against vancomycin-resistant Gram-positive bacteria, with high selectivity. This derivative is capable of disrupting preformed biofilms of MRSA. It also eradicates dormant bacterial populations, such as persisters and stationary phase cells of MRSA. This study bears particular significance, as it is one of the first studies to examine the effect of a semi-synthetic glycopeptide on the process of bacterial cell division. The lead derivative, AAV-qC10, leads to delocalization of the cell division protein, MinD, along with causing depolarization and permeabilization of the cell membrane. Notably, when tested in murine thigh infection model of MRSA, the lead derivative displayed superior efficacy than vancomycin in eradicating the superbug. The multiple modes of action of the derivative are responsible to halt resistance development in bacteria. This lead derivative, and the plethora of mechanistic studies performed with it, are first-of-its-kind and constitute an important contribution to the field.]

II. Konai, M. M.; Pakrudheen, I.; Barman, S.; Sharma, N.; Tabbasum, K.; Garg, P.; **Haldar, J.***. Cyclam-based Antibacterial Molecule Eradicates Gram-negative Superbugs with Potent Efficacy against Human Corneal Infection. *Chem. Commun. (Camb.)* **2020**, *56*, 2147-2150.

[In this article, we report the development of colistin-inspired, cyclam based antibacterial agents with potent activity against drug-resistant Gram-negative bacteria. Based on selectivity for bacterial killing over toxicity to mammalian cells, a lead molecule was isolated. This molecule, possessing the amino acid leucine, and the dodecanoyl long chain, is highly active against biofilms and stationary phase bacteria. It leads to depolarisation of the bacterial membrane, which may be a preliminary mechanism of its bactericidal action. This molecule, which is highly active against pathogen, not toxic to mammalian cells, and is stable in physiological fluids such as blood plasma, liver homogenate, etc. has been tested for its activity against corneal infection causing bacteria. Its efficacy has also been proven in an ex-vivo infection model of human cornea. The lead proves to be a promising drug-candidate as a potential cure for persisting ocular infections.]

III. Sarkar, P.; Samaddar, S.; Ammanathan, V.; Yarlagadda, V.; Ghosh, C.; Shukla, M.; Kaul, G.; Manjithaya. R.; Chopra, S.; **Haldar, J.*.** Vancomycin Derivative Inactivates Carbapenem-Resistant *Acinetobacter baumannii* and Induces Autophagy. *ACS Chem Biol*, **2020**, *15*, 884-889.

[This article reports the development of a semi-synthetic vancomycin derivative which has potent activity against vacomycin-resistant Gram-positive bacteria. This vancomycin analogue contains a quaternary ammonium centre, attached to its C-terminal, followed by a decyl chain attached through an amide bond. Unlike vancomycin, this novel vancomycin analogue is highly active against Gram-negative high-priority pathogen *A. baumannii* and its clinical isolates. It is highly efficient in tackling *A. baumannii* biofilms, as well as dormant stationary phase cells of the bacterium. This molecule also displays least in vitro and in vivo toxicity even through intravenous injection. Along with tackling Gram-negative pathogens as opposed to vancomycin, this analogue also tackles intracellular Gram-positive infections caused by MRSA. This activity is of particular importance, as intracellular MRSA infections are increasingly becoming a cause of concern. An interesting effect that this molecule displays is its ability to induce autophagy, a self-recycling cellular pathway, in mammalian cells, which may be aiding it intracellular clearance. This novel vancomycin analogue displays excellent therapeutic potential for further development and exploration.]

IV. Konai, M. M.; **Haldar, J.***. Lysine-Based Small Molecule Sensitizes Rifampicin and Tetracycline against Multidrug-Resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. *ACS Infect. Dis.* **2020**, *6*, 91-99.

[We have developed lysine-based small molecular antimicrobial peptide mimics in this study, which possess two lysine moieties at appended to the terminal primary amines of a symmetric triamine, and an alkyl chain appended to the central secondary amine. This molecule, easily synthesized in three simple steps, displays depolarization of the bacterial membrane. This effect shown by the molecule has been exploited in this study, as it leads to disruption of the functioning of antibiotic efflux pumps of the bacteria, which confer resistance against various antibiotics. Hence, we propose the use of this lead as a molecular adjuvant to resensitize different classes of antibiotics such as tetracycline and rifampicin against multidrug-resistant Gram-negative superbugs. The lead has demonstrated excellent potentiation, leading to a reduction of active concentration of the obsolete antibiotic by more than 30 times, in presence of compound. This molecule has been highly successful, not just in in vitro setting, but even in an in vivo mice model of burn wound infection. The combination can cure infections in mice caused by multidrug-resistant bacteria very effectively, indicating its promise as a potential drug candidate.]

V. Ghosh, C.; Sarkar, P.; Samaddar, S.; Uppu, D. S. S. M.; **Haldar, J.***. L-lysine based lipidated biphenyls as agents with anti-biofilm andanti-inflammatory properties that also inhibit intracellular bacteria. *Chem. Comm.*, **2017**, *53*, 8427-8430.

[This study reports the development of Lysine based lipidated biphenyls. These molecules possess two lipidated lysine molecules attached to a biphenyl. Excellent antibacterial activity was observed for these molecules against multi-drug resistant Gram-positive pathogens. From this series, the most selective lead was identified, which acts as selective membrane-active antibacterial agent and inhibits cell-wall

biosynthesis. The lead is not toxic towards mammalian cells. Along with activity against planktonic bacteria, the lead displays promising activity against biofilm-related infections and intracellular infections of mammalian cells. It also shows immunomodulatory properties at active concentration. When mammalian immune cells are treated with a strong bacterial antigen from Gram-positive bacteria, such as lipoteichoic acid, it elicits a strong immune response, leading to production of various proinflammatory cytokines. However, in presence of the lead molecule, this response induced by lipoteichoic acid is reduced, and TNF-α production is also suppressed. The antibacterial efficacy of this lead has also been tested in the in vivo setting, where it has displayed excellent potency in a murine model of MRSA infection.]

VI. Barman, S.; Konai, M. M.; Samaddara, S.; **Haldar, J.***. Amino-Acid Conjugated Polymers: Antibacterial Agents Effective against Drug-resistant *A. baumannii* with no Detectable Resistance. *ACS Appl. Mater. Interfaces*, **2019**, *11*, 33559−33572.

[The effect of amino acid (AMP's building block) incorporation in the design of AMP-mimicking polymeric material remains unexplored in the field of peptidomimetic antimicrobial agents. To explore this aspect, this study reports a class of amino-acid conjugated polymers (ACPs) synthesised by simple post polymer functionalization strategy. A detailed characterization was performed by using 2D proton-carbon correlation HSQC (DEPT edited) NMR spectroscopy. In general, the amino acid variation in the polymers had a profound effect on the antibacterial activity with negligible toxicity to mammalian cells. The highlight of this new class of polymeric materials was their potent activity against multidrug-resistant clinical isolates of *A. baumannii*. The optimized lead polymer was rapidly bactericidal and killed difficult-to-treat metabolically inactive stationary phase *A. baumannii* instantaneously. It was also able to eradicate preformed biofilms, which are almost untreatable with conventional antibiotic therapy. More importantly, no propensity of resistance development was detected even after multiple passages. This design was successful in tackling the various challenges associated with complex infections, indicating its superiority over conventional therapeutic options.]

VII. Yarlagadda, V.; Sarkar, P.; Samaddar, S.; **Haldar, J.***. Incorporation of Pyrophosphate Binding Ability to Vancomycin: A Strategy to Combat Vancomycin-resistant Bacteria. *Angew. Chem. Int. Ed.* **2016**, *27*, 7836-7840.

[This study reports the development of a potent alternative therapeutic for tackling vancomycin-resistant bacteria, in the form of a dipicolyl conjugated vancomycin derivative. This derivative displays 350-fold more in-vitro activity than vancomycin against vancomycin resistant *Enterococci* (VRE). The enhancement of activity occurs due to the binding of dipicolyl moiety to Zn^{2+} ion, which increases the binding of this derivative to pyrophosphate groups present in cell wall lipids while maintaining the inherent binding affinity for pentapeptide termini of cell-wall precursors. Furthermore, no resistance development was seen against this compound after several serial passages. Investigations of the in vivo activity revealed that the compound reduced Vancomycin resistant bacterial load by ~5 log at a concentration of 12 mg/kg in a murine model of VRB renal infection. This simple strategy of enhancing binding to pyrophosphate yielded an extremely active vancomycin derivative, with more than two orders of magnitude higher activity as compared to vancomycin, against VRE.]

VIII. Yarlagadda, V.; Manjunath, G. B.; Sarkar, P.; Akkapeddi, P.; Krishnamoorthy, P.; Shome, B. R.; Ravikumar, R.; **Haldar, J.***. Glycopeptide Antibiotic to Overcome The Intrinsic Resistance of Gram-negative Bacteria. *ACS Infect. Dis.*, **2015**, *1*, 469–478.

[This is a first of its kind study where we report lipophilic cationic vancomycin analogues which display potent activity against Gram-negative bacteria. Vancomycin is unable to penetrate through the outer membrane of Gram-negative bacteria, and hence, they display resistance to vancomycin. In our design, we have incorporated a hydrophobic alkyl chain, attached to vancomycin through a cationic charge bearing linker. This vancomycin analogue is able to permeabilize the outer membrane of Gram-negative pathogens and overcome their inherent resistance toward glycopeptides. The analogues also display membrane depolarization, along with inner and outer membrane permeation. These additional mechanisms may contribute to the analogues' excellent activity against a variety of multidrug-resistant clinical isolates such as *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa,* and *Acinetobacter baumannii*. We have proved the intracellular accumulation of our analogue in these bacteria, and also reaffirmed its applicability as a therapeutic by validating its efficacy in the in vivo setting. The analogue displays efficacy far superior to vancomycin, and comparable to last resort antibiotic colistin in a murine thigh-infection model against carbapenem-resistant *A. baumannii*. However, our analogue offers better prospects as it does not induce resistance development even after 20 passages, while colistin induces a 32-fold increase in its MIC in the same setting. All these characteristics posit our novel lipophilic cationic vancomycin analogue as an emerging alternative to address challenging and devastating multidrug-resistant Gram-negative infections.]

IX. Ghosh, C.; Manjunath, G. B.; Akkapeddi, P.; Yarlagadda, V.; Hoque, J.; Uppu, D. S. S. M.; Konai, M. M.; **Haldar, J.***. Small Molecular Antibacterial Peptoid Mimics: The Simpler The Better! *J. Med. Chem*. **2014**, *57*, 1428-1436.

[This article reports the development of simple, amino acid-based antibacterial molecules, which display potent activity against a broad range of drug-resistant bacteria. From a structural perspective, the design is extremely simple, where two positive charges contributed by the amino acid lysine and hydrophobicity, brought in by an aromatic core and an alkyl chain, are formulated in three simple steps. The lead molecule from this series possess a naphthyl group and a decyl alkyl chain. It has been identified to be the most selective one, with high antibacterial activity, and least toxicity towards mammalian cells. This molecule is an extremely effective therapeutic, as it eradicates highly pathogenic multidrug-resistant Gram-positive and Gram-negative bacteria, including the nosocomial pathogen *P. aeruginosa*, the top priority pathogen vancomycin-resistant *E. faecium*, etc. This molecule, unlike naturally occurring antimicrobial peptides, is highly resistant to enzymatic cleavage, and retains its activity in complex biological fluids such as blood plasma. It works particularly by disrupting the bacterial cell membrane, and destabilizing its potential. It also displays rapid killing kinetics, effectively eradicating ~6 log bacteria within 60 minutes. Altogether, these simple designs present immense potential as antibacterial therapeutics.]

X. Ghosh, S.; Mukherjee, R.; Basak, D.; **Haldar, J.***. One-Step Curable, Covalently Immobilized Coating for Clinically Relevant Surfaces That Can Kill Bacteria, Fungi, and Influenza Virus. *ACS Appl. Mater. Interfaces*, **2020**, *12*, 27853–27865.

[In the current scenario of COVID-19, development of antimicrobial surface coatings for PPEs, and other biomedical surfaces will definitely play an important role in prevention of spread of infectious diseases in hospitals and community, including viral infections. Towards the same direction, we report here the development of a simple, highly membrane-active surface coating, with potent ability to reduce transmission of multidrug-resistant bacteria, fungi as well as the Influenza virus. This coating is based on two organo- and water-soluble small molecules, quaternary benzophenone-based ester and quaternary benzophenone-based amide, which undergo cross-link on the coated surface under the action of UV irradiation. The coating leads to immediate killing of drug-resistant pathogens methicillin-resistant *Staphylococcus aureus* (MRSA) and fluconazole-resistant *Candida albicans* upon contact. It also demonstrates 100% inactivation of the highly infectious and prevalent enveloped respiratory virus Influenza. The antimicrobial activity of the surface also extends to metabolically inactive stationary phase MRSA, owing to its membrane active nature. Once the surface undergoes hydrolysis, the coating turns displays antifouling properties also. This coating can be covalently attached to a variety of surfaces like cotton, polyurethane, polyethylene etc. with a short UV treatment. To the best of our knowledge, this is one of the first reports of a multifunctional coating with potent efficacy against bacteria, fungi as well as viruses, indicating its strong potential for commercial development.]