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

Total Publications: 108 Research Articles (84 as corresponding author) + 13 Review articles (12 as corresponding author) + 9 Book Chapters (8 as corresponding author)

Citations: 5971, **h-index:** 44, **i-10 index:** 87 (According to Google Scholar as on 24th August, 2023)

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 the 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. Sarkar, P.; De, K.; Modi, M.; Dhanda, G.; Priyadarshini, R.; Bandow, J. E.; **Haldar, J.***. Next-generation membrane-active glycopeptide antibiotics that also inhibit bacterial cell division. *Chem Sci*, **2023**, *14*, 2386-2398.

[In our pursuit for the search of next-generation membrane-active glycopeptide antibiotics, in this study we report a new derivative of vancomycin and explored the antibacterial mechanisms beyond the conventional notion of D-Ala-D-Ala binding. These modified vancomycin derivatives show several alterations in the bacterial cells, which facilitate inactivation of the pathogens. A detailed study of the structure and activity profile gives alkyl-cationic substitutions an edge over aryl analogs. The lead candidate, $VanQAmC_{10}$ shows a significant extent of depolarization and permeabilization of bacterial membrane. Interestingly, $VanQAmC_{10}$ shows retardation of growth during cell division, which is the first of its kind observation setting $VanQAmC_{10}$ apart from other glycopeptide antibiotics. The compound also hampers the distribution of MinD, a protein which has an integral role in cell division regulation machinery. Not only *in-vitro*, $VanQAmC_{10}$ showed superior activity in a mice model of thigh infection. VanQAmC10. Overall, this study investigates multiple mechanisms of

action of a novel vancomycin derivative which contribute to the negligible resistance induction and superior antibacterial properties as compared to the parent drug.]

III. 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.]

IV. Barman, S.; Dhanda, G.; Naik, P.; Mukherjee, R.; Jolly, L.; Joseph, J.; **Haldar, J.***. Multi-functional small molecules with temporal charge-switchability tackle infection and inflammation. *Adv. Therap.*, **2022**, *53*, 2100234.

[This article introduces an innovative category of versatile amino acid-conjugated small antibacterial molecules that effectively address complicated infections and associated inflammation. These molecules demonstrate a wide-ranging bactericidal effect against bacteria that are resistant to multiple drugs. The lead molecule, ASAM-10 incorporating phenylalanine, efficiently targets bacterial dormant subpopulations, biofilms, and intracellular pathogens simultaneously. A noteworthy feature of this work is its ability to mitigate the toxicity concern linked to cationic lipopeptides such as colistin, achieved through a temporal charge shift from cationic to zwitterionic due to the breakdown of labile ester connections after furnishing desired antibacterial action. The significant decrease in the expression of pro-inflammatory cytokines (IL-6, IL-8, TNF-$\boldsymbol{\alpha}$, and IL-1$\boldsymbol{\beta}$) in infected macrophages upon ASAM-10 treatment underscores its potent anti-inflammatory properties. Not only in-vitro, administering ASAM-10 in a mice with thigh infection showed a substantial reduction in bacterial load (2 Log CFU/g). Collectively, this novel class of multifunctional molecules demonstrates its safety and promises advanced therapeutic potential in addressing complex bacterial infections and inflammation.]

V. 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.]

VI. Dhanda, G.; Mukherjee, R.; Basak, D.; **Haldar, J.***. Small-Molecular Adjuvants with Weak Membrane Perturbation Potentiate Antibiotics against Gram-Negative Superbugs. *ACS Infect. Dis.*, **2022**, *8*, 1086–1097.

[In this work, we meticulously explore the structural parameters for the formation of an optimum membrane-targeting antibiotic adjuvant using norspermidine as a model compound. By appending different hydrophobic groups to its secondary amine, it's observed that cyclic hydrophobic moieties show good potentiating ability and are devoid of toxicity or activity. Adamantane and aryl-functionalized derivatives (NAda and NDiphe) exhibit as high as 4096-fold potentiation of multiple classes of antibiotics toward critical Gram-negative superbugs, proving to be the optimum adjuvant. The mechanism of potentiation consists of weak outer membrane permeabilization, membrane depolarization, and efflux inhibition. The lead adjuvants show a significantly increased accumulation of antibiotics in NDM-1-producing bacteria E. coli R3336 and K. pneumoniae R3934. This work is the first of its kind highlighting the importance of "weakly perturbing the membrane" by incorporating cyclic hydrophobic moieties in the chemical design.]

VII. Uppu, D. S. S. M.; Konai, M. M. K.; Baul, U.; Singh, P.; Siersma, T. K.; Samaddar, S.; Vemparala, S.; Hamoen, L. W.; Narayana, C.; **Haldar, J.***. Isosteric substitution in cationic-amphiphilic polymers reveals an important role for hydrogen bonding in bacterial membrane interactions. *Chem. Sci.* **2016**, *7*, 4613-4623.

[In our work towards development of peptidomimetic antimicrobial polymers, we have developed numerous water-soluble, antimicrobial polymers employing poly(isobutylene-alt-maleic anhydride), chitosan and polyethyleneimine backbones. In these libraries of cationic polymers, we have exhaustively attained the importance of amphiphilicity, which dictates the binding of cationic polymers to the negatively charged bacterial membrane. In this work, we investigate the role of hydrogen bonding in determining the specific interactions between the polymers and bacterial membrane. Through the analysis of a isosterically substituted series of poly(isobutylene-alt-N-alkyl maleimide) based amphiphilic polymers, we show that amide polymers show higher antibacterial activity compared to their ester analogues. A thorough understanding through Raman spectroscopic and biophysical studies show that amide-containing polymers show formation of hydrogen bond with lipid molecules, which is also substantiated by molecular simulations. Overall, for the first time this work provides evidence for the role of hydrogen bonding in bacterial membrane interactions.]

VIII. 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 possesses 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.]

IX. Ghosh, S.; Mukherjee, R.; Mahajan, V. S.; Boucau, J.; Pillai, S.; **Haldar, J.***. Permanent, Antimicrobial Coating to Rapidly Kill and Prevent Transmission of Bacteria, Fungi, Influenza, and SARS-CoV-2. *ACS Appl. Mater. Interfaces*, **2022**, *14*, 42483–42493.

[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 active surface coating, with potent ability to reduce transmission of multidrug-resistant bacteria, fungi as well as the Influenza and SARS-CoV-2 viruses. This coating is based on a quaternary benzophenone-based small molecule, which can cross-link on a wide range of surfaces upon brief UV irradiation. The coated surfaces show very rapid inactivation of pathogens thereby diminishing their transmissibility.]

X. Dey, R.; Mukherjee, R.; **Haldar, J.***. Photo-crosslinked antimicrobial hydrogel exhibiting wound healing ability and curing infections in vivo. *Adv. Healthc. Mater.* **2022**, *11*, 2200536.

[In this report, we engineer an intrinsically antimicrobial hydrogel (HyDex) in a one-pot UV crosslinking technique, employing dextran methacrylate, polyethylene glycol diacrylate, and cationic lipophilic methacrylate with varied hydrophobic chain. The optimized hydrogel exhibits potent antimicrobial efficacy against multidrug-resistant Gram-positive and Gram-negative bacteria as well as against pathogenic fungus *Candida albicans*. A major problem, traumatic or wound-associated hemorrhage is addressed rapidly using this hydrogel in a mice liver puncture model. The hydrogel kills carbapenem-resistant Acinetobacter baumannii in a murine model of burn wound infection with >99% reduction in bacterial burden, with accelerated wound healing in rat deep wound model.]