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Statement of Research Achievement

Our laboratory employs a combination of structural biology, biochemistry, and synthetic chemistry skills as versatile tools to develop solutions for antibiotic resistance. Antibiotic resistance is a global problem that is increasing at an alarming rate with pathogens becoming resistant to even the last line of drugs. To tackle this problem of drug resistance, it is imperative to focus on the origins of resistance itself. Our contributions in the arena of antibiotic resistance has resulted in development of drug candidates that can work as combination therapy and when used with existing antibiotics can ***reverse resistance***. Our strategy revolves around sensitizing drug-resistant bacteria towards existing antibiotics by focusing on elucidating mechanisms that render normal bacteria resistant to antibiotics. The first area of exploration involved efflux pump regulators, TetRs, which play a vital role in expelling antibiotics from cells, resulting in reduced antibiotic concentrations below effective levels. The X-ray structure of the tetracycline receptor (TetR) in complex with DNA from the antibiotic-producer organism, *Streptomyces coelicolor (**Nucleic Acid research 2014***), revealed the allosteric mechanisms between antibiotic and DNA binding sites. Based on this information, the development of efflux pump blockers can be envisioned that stabilizes the TetR-DNA complex and thereby avoid activation of efflux pumps. This strategy will reverse resistance by increasing antibiotic concentrations in the cells thus, re-sensitizing the pathogens towards existing antibiotics. Our work paved the way towards understanding evolutionary links between these regulators and helped shed light on how cellular antibiotic concentration can be regulated (***NAR2014, JPC2014, BBA2015, JSB2017)***. Subsequently, our group solved structures of unique TetRs from *Streptomyces fradiae,* another antibiotic producer, that further helped decode the various architectures and mechanisms by which drug regulation occurs (***JBC 2017)***.

The other prominent mechanism of resistance present in several pathogenic strains is the methylation of ribosomes in the protein exit tunnel which renders the organism resistant to more than 50 different antibiotics belonging to the macrolide, lincosamide, and streptogramin class. This methylation is enabled by a class of ribosomal methyltransferases, only present in multi-drug resistant (MDR) pathogens that selectively perform post-translational modification of ribosomes leading to low affinity for these drugs. A combination of crystal structures of these enzymes along with methylation efficiency experiments with several chimeric enzyme constructs helped us to decipher the targeting determinants (***JACS 2019)***. We further solved the cryo-EM structure of the methyltransferase in complex with the 30S ribosome. This breakthrough helped us to unravel specificity determinants at the ribosomal level (***ACS Chem Bio, 2022***). Recently, we have been able to establish allosteric sites, exclusively present in methyltransferase that are now being used to develop combination therapy candidates (***JBC 2022***). A combination of virtual and high throughput screening has enabled us to find drug molecules that are able to re-sensitize MDR pathogens to existing antibiotics and reverse resistance. We believe this therapy being developed in our laboratory will really revolutionize the way we perceive resistance and are in the process of patenting some of the top drug candidates.

In the direction of finding new drug targets, the goal is to study essential enzymes. Our focus is on nucleobase pathway enzymes that are essential for survival. Our recent work on understanding the allosteric regulation in the purine salvage pathway has brought out key aspects of allosteric communication and molecular tunnel formation that are evolutionarily variant in humans versus bacteria (***Science Advance 2020, ACS Catalysis 2022***). This aspect can be further exploited to design strategies that can target protein-protein interaction interfaces in a species-specific manner. Further, early work on nucleobase deaminases (***Biochemistry2013a, Biochemistry2013b***) and recent work in ***JACS 2017***, ***JSB 2021*** led us to discover a remarkable new enzyme, exclusively found in *Mycobacterium,* which confers innate resistance towards aza-scaffold of drugs. Here, the X-ray structure of this novel enzyme and subsequent structures with substrate and their analogs aids in understanding function. It was established that this enzyme scans for mutagenic bases and eliminates them from the cells. Thus, by targeting this newly discovered pathway one can sensitize these resilient organisms towards mutagenic base harboring drugs (***JACS 2017)***.

In addition, for my contributions to projects with societal relevance and to break the barriers in the field of structural biology where we can look at large complexes, and in cellular environments map structure, I have received as a principal investigator a grant (5 million US dollars) from SERB, India to set up the state-of-the-art ***cryo-electron- microscopy center at IIT Bombay.*** Along with these, I have been awarded the ***DBT-Welcome Trust Fellowship (2019)*** for further research in antibiotic resistance, the ***Women's BioScientist award (2018)*** by DBT, elected as a member of the prestigious ***National Academy of Sciences in 2019,*** and the ***IIT Bombay Impactful Research Award (2020).*** In conclusion, I would like to reiterate that our efforts are to bridge basic and applied sciences, which is the need of the hour to tackle the complicated global problems of antibiotic resistance.

Sincerely,

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