Abstract for public

Antibiotics are small molecules widely used to treat pathogenic infections. They form a significant part of our arsenal in combatting infectious diseases, despite the evolution of new vaccine candidates for many diseases. However, the rate of development of new drugs is a tedious and slow process, as many potential molecules get rejected due to poor pharmacodynamic and toxicological properties. Antibiotics work by either decreasing the rate of growth of microorganisms or by cell death. However, antimicrobial resistance is rapidly evolving as a public health and safety threat that is already affecting millions of patients worldwide. If not managed, antimicrobial resistance has the potential to be the next great public health disaster that would create huge economic burden worldwide and claim millions of lives. Infectious diseases that are known to be treatable, can turn lethal as antibiotics cease to function. Antimicrobial resistance arises naturally through natural selection as a necessary means of survival tool to protect the organism against toxic molecules often produced by other microorganism. However, irresponsible and unjust use of antibiotics by humans increases the exposure of microorganisms to these compounds often at sub lethal doses, thus creating a survival pressure that accelerates development and spread in antimicrobial resistance. Microorganisms exhibit remarkable genetic plasticity with the capability of passing over DNA sequences, known as mobile genetic elements that often code for antimicrobial resistance factors. This secondary transmission can often be inter-species thus leading to a vast number of organisms turning resistant against antibiotics.

The molecular details of how antibiotics work vary greatly and they have a wide range of targets, that are critical cellular machinery necessary for microbial survival. One such critical cellular machinery is DNA gyrase, an enzyme whose function is necessary for both microbial cells to survive and multiply. The mechanism of how the Gyrase machinery works is still not completely understood and requires further investigation. A number of commonly used antibiotics bind to this enzyme to stall the chemical reaction that it catalyzes and this leads to disruption of the genetic code of the pathogen, leading to its death. One such protein that is often spread by mobile genetic elements in critical pathogens is Pentapeptide Repeat Proteins (PRPs). These proteins look very similar to DNA and interacts with DNA gyrase in a manner that the Gyrase gets rid of bound antibiotics. Once the antibiotics are rid of, the DNA break is resealed by the DNA Gyrase and thus the organism survives. PRPs, though are similar structurally to each other, and interacts with the same Gyrase, they have minor structural differences. Studies have shown that different PRPs cause resistance against different classes of antibiotics. In this study, we want to understand the reason behind this specificity as we are trying to design a therapeutic agent that would work against Pentapeptide Repeat Proteins. Disruption of PRP mediated antimicrobial resistance would allow antibiotics that stopped working, to be clinically effective again. One such example of this approach is the use of ß-lactamase inhibitors against ß-lactamases which are resistance factors that degrade antibiotics similar to Penicillin. We wish to study the interaction of all these different PRPs with Gyrase using tools of Structural Biology, chiefly Cryo-Electron Microscopy. We have already gained experience studying PRP mediated resistance against Fluoroquinolone antibiotics and have had success obtaining atomic structures. Now, we wish to expand our understanding of atomic interactions involved in albicidin and Microcin B17 resistance. These studies would help us identify if there are any similarities between these mechanisms despite the differences. We would like to exploit these similarities to design one therapeutic strategy that would be effective against multiple classes of PRP-mediated drug resistance.