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Overcoming antibiotic resistance: Inhibition of ld-transpeptidation in multi-drug resistant pathogens

Multidrug-resistant microorganisms produce infections that are hard to treat or may even be untreatable with conventional antimicrobials. *Mycobacteria tuberculosis (Mtb), Clostridae difficile (Cd)*, and ESKAPE pathogens are capable of developing resistance to not only clinical antibiotics, but to the last resort (such as carbapenems) as well. The development of novel treatment options to replace antibiotics that lost their effectiveness and new antibiotic targets to circumvent target-specific resistance, which has emerged against every antibiotic class, are high priorities.The development of the necessary new antibiotics through trial-and-error is a costly and time-consuming proposition. Structure-based drug design accelerates discovery by linking structural information and computational techniques. The targeting late stages of bacterial cell-wall biosynthesis remains a sound strategy. The peptidoglycan of *Mtb, M. abscessus*, and *Cd* during stationary growth is synthetized by LD-transpeptidases (LDTs), different enzyme than DD-transpeptidases (Penicillin-binding proteins) the primary target of β-lactams. This difference contributes to these pathogens resistance to β-lactams. We are investigating the molecular structures of *Mtb* LDTs and its complexes with carbapenems. Structural evidence from these studies suggests that the catalytic site flexibility dynamically accommodates ligands larger that than the geometric volume of the site observed in the crystallographic structure. Thus, inhibitors binding to LDTs can involve transient active-site conformations unobserved in the time-averaged crystallographic structure. We are developing methods to seek LDTs inhibitors targeting accessible dynamic states of these enzymes in drug-resistant pathogens to obtain antibiotic leads. In this talk, I'll present preliminary results of our work targeting essential *Mtb* transpeptidase, LdtMt2.

Biography

Mario A Bianchet has completed his PhD from National University of La Plata, Argentina and performed his Postdoctoral training at Johns Hopkins School of Medicine where he joined as Assistant Professor in the Department of Neurology in 2011. He is a Structural Enzymologist and has participated in several seminal structural and mechanistic studies of macromolecular systems of biomedical interest including cell-wall biosynthesis: LD-transpeptidases and their complexes with carbapenems. In addition, he has valuable contributions to diverse fields, including bioenergetics: F1-ATPase, xenobiotic-response: NADPH:Quinone oxidoreductases, DNA-repair: Uracyl-glycosylase/inhibitors, carbohydrate-recognition: animal lectins, resulting in 70 publications in reputed journals.

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