

## Drug Resistant Tuberculosis and development of new inhibitors

**Abstract:** Antibiotic resistance has been increasing at an alarming rate due to their indiscriminate use. The United Nations and the World Health Organization (WHO) have considered this significant and worsening health challenge. Tuberculosis (TB), one of the most deadly bacterial diseases, has been declared as number one killer by WHO, even surpassing HIV/ AIDS. New drugs that can kill drug-resistant TB by inhibiting essential but unexploited pathways could provide a solution to control global TB. Our group has identified a novel enzyme that *Mycobacterium tuberculosis* (the bacteria that causes TB) uses to synthesize its peptidoglycan (PG), a layer that is present in all bacteria and essential for their survival. This enzyme, a L,D-transpeptidase, generates 3→3 transpeptide linkages and completes PG synthesis. Historically, the final step of PG synthesis was known to be catalyzed by only D,D-transpeptidases (also known as Penicillin Binding Protein) but we and other groups have shown that this is incorrect. While the D,D-transpeptidases are inhibited by  $\beta$ -lactams (which comprise >50% antibiotics of all antibiotics used globally), L,D-transpeptidases are unique and not generally susceptible to all  $\beta$ -lactams. We have shown that the carbapenem subclass of  $\beta$ -lactams are distinctly effective in inhibiting L,D-transpeptidases amongst all  $\beta$ -lactams. We further unveiled the structural and molecular details of interactions of carbapenems with L,D-transpeptidases from *M. tuberculosis* and used these Structure Activity Relationship data to design, synthesize and evaluate new carbapenems with potent antibacterial activity. Our new and evolved carbapenems are not only potent *in-vitro* but also exhibit high potency in the mouse model of TB. We also have explored the mechanism of carbapenem drug resistance in *M. tuberculosis* as the emergence of drug-resistant TB is inevitable to these carbapenems in future.