Poster Presentation

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Structural basis of mycobacterial inhibition by natural products targeting ClpC1

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Unfolded or damaged proteins in a cell must be targeted for degradation before they start accumulating and reach toxic levels. In bacteria, chaperones and proteases perform this important protective and restorative role. Caseinolytic protease-associated chaperone C (ClpC) is one such protein that performs the function of cellular protein quality control primarily through its association with ClpP1P2 protease core, wherein the chaperone aids in ATP-dependent unfolding of protein substrates to be degraded by the protease machinery. ClpC belongs to the family of AAA+ HSP100 proteins. Three structurally different lead compounds from Actinomycetes have recently been reported to specifically kill mycobacteria (but not other Gram-positive bacteria) by targeting ClpC1 protein. MtClpC1 is an essential protein for mycobacterial growth and is very distinct from the targets of other existing anti-TB drugs. The reported natural products targeting ClpC1 were all found to be effective against drug susceptible as well as MDR mycobacterial strains. They seem to elicit their activity by binding to the N-terminal domain of ClpC1. Here we discuss the findings from our studies on MtClpC1 in complex with the natural product compounds and explain why these target mycobacteria, but not other bacteria.

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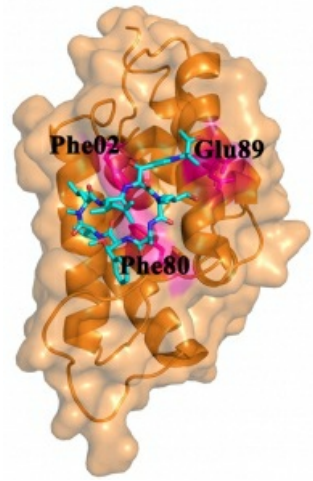

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