

Poster Presentation

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Crystal Structure of AcrB Complexed with Linezolid at 3.5Å Resolution

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We present the crystal structure of AcrB in complex with Linezolid[1]. AcrB is an inner-membrane Resistance-Nodulation-Division efflux pump and is part of the AcrAB-TolC multidrug-resistance tripartite efflux system in E. Coli. Crystal structures of AcrB by itself as well as several drug-bound complexes have been structurally characterized. Linezolid is an approved oxazolidinone antibiotic used for the treatment of serious infections caused by Gram-positive bacteria that are resistant to other antibiotics, and has been called a "reserve antibiotic", a drug of last resort against potentially intractable infections. This antibiotic inhibits bacterial protein synthesis by specifically binding to the 50S ribosomal subunit. Linezolid has no clinically significant effect on most Gram-negative bacteria. This is thought to be a result of relatively low intracellular concentration of Linezolid due to efflux, but there is no direct evidence yet to support this hypothesis. This membrane protein-drug complex shows that an antibiotic specific to Gram-positive bacteria can also bind an efflux pump from E. coli, a Gram-negative bacterium. The crystal structure of AcrB and Linezolid complex reveals that Linezolid binds to the A385/F386 loops of the symmetric trimers of AcrB in the same fashion as several other antibiotics that are extruded by efflux pumps. A conformational change of a loop in the bottom of the periplasmic cleft is also observed.

[1] L.-W. Hung, H.-B. Kim, S. Murakami et al., *Journal of Structural and Functional Genomics*, 2013, 14(2), 71-75

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