

Poster Presentation

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A catalytic switch uncovered in gentamicin resistance kinase APH(2'')-Ia

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The APH(2'')-Ia domain of the bifunctional aminoglycoside resistance enzyme AAC(6')-Ie/APH(2'')-Ia confers high-level resistance to aminoglycoside antibiotics. Crystal structures of this kinase domain in complex with GTP analogues and acceptor substrates have uncovered a surprising conformational bistability of the GTP substrate, which may reduce futile hydrolysis of the cofactor by the enzyme. This conformational switch is influenced by the binding of aminoglycosides, and may represent an adaptive feature of the enzyme, improving its evolutionary fitness in bacterial populations. This mechanism combines with a remarkable flexibility observed in the binding of diverse aminoglycoside substrates to make this enzyme a formidable antibiotic resistance machine.

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