Poster Presentation

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Inhibitors of the DNA-cleavage gate of bacterial type IIA topoisomerases

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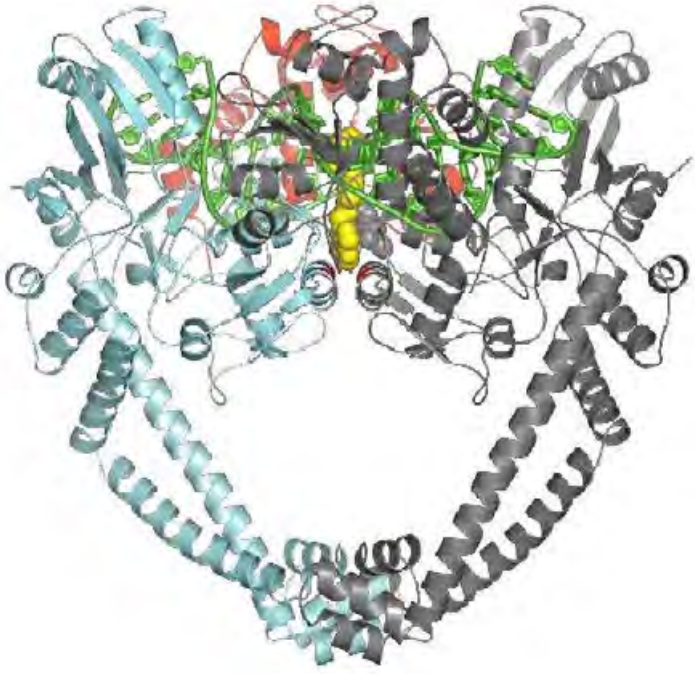
Type IIA topoisomerases resolve topological problems in DNA by making a double-stranded break in one DNA segment, passing another DNA duplex through this break, and then resealing the break. Drugs (such as the widely used fluoroquinolone antibacterials and anti-cancer compounds such as etoposide) that stabilize double-strandedly cleaved DNA complexes with type IIA topoisomerases are cytotoxic. In GlaxoSmithKline a new class of novel bacterial topoisomerase inhibitors (NBTIs) have been developed. A 2.1Å crystal structure of a complex of GSK299423 with DNA and S. aureus DNA gyrase showed how the NBTI inhibits the enzyme by interacting with both the DNA and the protein. A pocket occupied by the compound in the protein (at the dimer interface) is absent in the apo structure, while the pocket occupied by the compound in the DNA has been formed by the enzyme stretching and untwisting the DNA between the two active sites. The NBTI structure has trapped a pre-cleavage complex of the enzyme, before the four base-pair double stranded break has occurred, and the structure gives insights into the role of metal ions in the cleavage mechanism of type IIA topoisomerases. Stuctures suggest how relatively small movements at the active sites (for example an ~3Å movement of a magnesium ion) can cause the cleavage of phosphate ester bonds and are coupled to the large domain movements involved in the catalytic cycle of these conformationally flexible enzymes. The binding site for the NBTI is close to but distinct from those for fluoroquinolones. Structures shows how the fluoroquinolone interacts with both the protein and the DNA by binding a non-catalytic magnesium ion and four associated waters. This provides a structural explanation for both fluoroquinolone resistance mutations and SAR (structure-activity relationships). Mechanistic implications of recent structural studies will be discussed.

[1] *B.,Bax, P.Chan, D.Eggleston, et al., Nature, 2010, 466, 935-940.,* ***[2]*** *Chan, P. F., Huang, J. , Bax B. , & Gwynn, M. N., 2013 'Recent developments in inhibitors of bacterial type IIA topoisomerases.' in: Antibiotics: Targets, mechanisms and resistance (Wiley)*



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