Poster Presentations

[MS9-P04] Insights into the mechanism for DNA capture and transport by topoisomerase II provided by the high- resolution structure of an 'open' topoisomerase II-DNA complex. Ivan Laponogov[1,2], Dennis A. Veselkov[1], Isabelle M.-T. Crevel[2], Xiao-Su Pan[2], L. Mark Fisher[2*] and Mark R. Sanderson[1*]

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Type II topoisomerases perform essential roles in DNA replication, chromosome segregation, and recombination[1-3] and are important antibacterial and anticancer targets[4-7]. Type II topoisomerases regulate DNA supercoiling and chromosome segregation via an ATP-driven DNA strand passage mechanism. However, the paucity of structures for native full-length proteins has been a significant obstacle in defining the reaction pathway. Here we present for the first time a high resolution X-ray crystal structure of an 'open clamp' complex of a type II topoisomerase, the key complex engaged in DNA capture and transport. The topoisomerase IV structure shows the disposition and conformation of all three gates required for catalysis and reveals a novel DNA binding site providing new insight on DNA bending and distortion at the DNA gate. We show that the open ATPase gate (N-gate) is oriented so that both the gate-DNA and transported DNA duplexes can access the enzyme without hindrance. Our data indicate that the ATPase domains pivot about flexible hinges to capture the incoming DNA. The open clamp state is the starting point for the topo IV reaction cycle, and its structure allows us to draw the overall mechanistic pathway by which coordinated minimal movement of domains results in DNA strand passage. The work has important implications in understanding type II topoisomerases as complex biological machines.

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