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Actinomycin D binding mode reveals the basis for its potent HIV-1 and cancer activity THAYAPARAN PARAMANATHAN, IOANA D. VLADESCU, MICAH J. MCCAULEY, Northeastern University, Boston, MA, IOULIA ROUZINA, University of Minnesota, Minneapolis, MN, MARK C. WILLIAMS, Northeastern University, Boston, MA — Actinomycin D (ActD) is one of the most studied antibiotics, which has been used as an anti-cancer agent and also shown to inhibit HIV reverse transcription. Initial studies with ActD established that it intercalates double stranded DNA (dsDNA). However, recent studies have shown that ActD binds with even higher affinity to single stranded DNA (ssDNA). In our studies we use optical tweezers to stretch and hold single dsDNA molecule at constant force in the presence of varying ActD concentrations until the binding reaches equilibrium. The change in dsDNA length upon ActD binding measured as a function of time yields the rate of binding in addition to the equilibrium lengthening of DNA. The results suggest extremely slow kinetics, on the order of several minutes and 0.52 $\pm$ 0.06 μM binding affinity. Holding DNA at constant force while stretching and relaxing suggests that ActD binds to two single strands that are close to each other rather than to pure dsDNA or ssDNA. This suggests that biological activity of ActD that contributes towards the inhibition of cellular replication is due to its ability to bind at DNA bubbles during RNA transcription, thereby stalling the transcription process.

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