Researchers demonstrate novel method for studying the DNA binding of small molecules

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Northeastern University professor Mark C. Williams and colleague Ioana Vladescu have discovered a novel method for studying the DNA binding of small molecules with unprecedented accuracy. Their paper, titled “Quantifying force-dependent and zero-force DNA intercalation by single-molecule stretching,” has been published in the May 2007 issue of the prestigious *Nature Methods*.

Because molecules that bind through intercalation (a type of binding) may interfere with important biochemical processes in replicating cells, this method may be a useful tool for rational anti-cancer, AIDS and other disease drug design.

“In order to develop new drugs to treat cancer and other diseases, scientists need to better understand if and how these drugs will bind to DNA,” says Williams. “This new method allows us to examine intercalation in unprecedented and exquisite detail.”

Williams and colleagues used single DNA molecule stretching to investigate DNA intercalation by ethidium and three ruthenium complexes. By measuring ligand-induced DNA elongation at different ligand concentrations, they determined the binding constant and site size as a function of force. Both quantities depend strongly on force and, in the limit of zero force, converge to the known bulk solution values, when available.

This approach allowed the team, comprised of Williams, Vladescu and

colleagues Micah McCauley, Megan Nunez and Ioulia Rouzina to distinguish the intercalative mode of ligand binding from other binding modes and allowed characterization of intercalation with binding constants ranging over almost six orders of magnitude, including ligands that do not intercalate under experimentally accessible solution conditions. As ligand concentration increased, the DNA stretching curves saturated at the maximum amount of ligand intercalation. The results showed that the applied force partially relieves normal intercalation constraints. The team also characterized the flexibility of intercalator-saturated dsDNA for the first time.

Williams and his colleagues are continuing their research and plan to start testing actively used cancer drugs in the near-term.

Source: Northeastern University