# Structure of enzyme unravelled providing basis for more accurate design of chemotherapeutic drugs

November 15 2012

A group of researchers at the University of California, Berkeley have for the first time described the structure of the active site core of topoisomerase II alpha, an important target for anti-cancer drugs.

The type II topoisomerases are important enzymes that are involved in maintaining the structure of DNA and chromosome segregation during both replication and transcription of DNA. One of these enzymes, topoisomerase II alpha, is involved in the replication of DNA and cell proliferation, and is highly expressed in rapidly dividing cancer cells. As such, this enzyme is the primary target of chemotherapeutic small molecule inhibitors such as etoposide. A major drawback to the use of these drugs is their association with secondary malignancies in some patients—a side effect believed to be caused by a cross-reaction with topoisomerase II beta, another member of this family that is involved in DNA transcription.

In their study the group of researchers, led by Professor James Berger, report securing the structure of the active site core of topoisomerase II alpha in complex with DNA. They describe the conformational changes undergone by the enzyme during DNA binding and cleavage. While the structure of etoposide-inhibited topoisomerase II beta has been previously established by others, this is the first time similar structural information has been available for topoisomerase II alpha. Comparing the structures of these enzymes could assist in the design of more

specific etoposide-like drugs, and reduce the risk of secondary malignancies.

"We hope this work will lead to an improved understanding of the mechanisms by which select small-molecule agents inhibit type II topoisomerase function, as well as help guide the development of new or improved antibacterial and anticancer drugs against enzymes of this class," said Professor Berger.

In a commentary accompanying the article, Professor N. Patrick Higgins of the University of Alabama, states that, together with the previously published structure of topoisomerase II beta, "...these two structures provide key information that will be relevant to understanding how these closely related proteins perform different roles during cell growth and tissue development. The newly described structure could also provide the basis for the design of more selective drugs, with a lower risk of side effects."

**More information:** The article is "The Structure of DNA-Bound Human Topoisomerase II Alpha: Conformational Mechanisms for Coordinating Inter-Subunit Interactions with DNA Cleavage" by Timothy J. Wendorff, Bryan H. Schmidt, Pauline Heslop, Caroline A. Austin, and James M. Berger (doi:10.1016/j.jmb.2012.07.014). The article appears in *Journal of Molecular Biology*, Volume 424, Issue 3-4, pages 109 (7 December 2012)

Provided by Elsevier