Dynamic model of a type II DNA topoisomerase and design of catalytic inhibitors as anticancer agents

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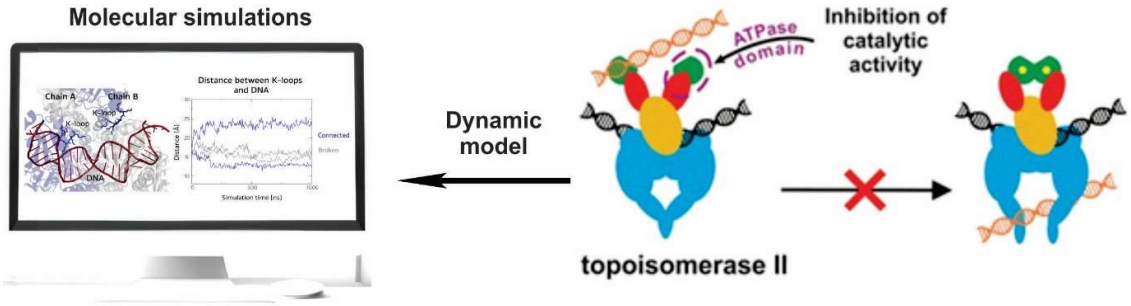
Type II DNA topoisomerases are biological nanomachines that regulate topological changes in the DNA molecule and are considered prime targets for anticancer drugs. Despite intensive research, many atomic details about their mechanism of action are still unknown. In our research, we are using a combination of computational biochemistry and a range of experimental techniques to better understand these complex molecular motors and to develop catalytic inhibitors of human topoisomerase IIα that would circumvent the limitations of topoisomerase poisons such as etoposide and doxorubicin that are routinely used in chemotherapy [1,2].

Based on structural and biochemical data, classical molecular simulations and multiscale QM/MM calculations were used to create a dynamic model of a type II topoisomerase. This included a study of the catalytic mechanism of ATP hydrolysis [3] and molecular simulations of different conformational states/steps in the topo II catalytic cycle. Point mutation study further complemented the performed computational work. Overall these models improved the mechanistic understanding of how the type II topoisomerase can alter DNA topology and provided guidelines for new subsequent experiments.

Our research is also focused on the development of catalytic inhibitors of human topoisomerase IIα targeting the ATP binding site. By structurally comparing the ATPase domains of human and bacterial II topoisomerases, we discovered a series of substituted 4,5'-bithiazoles that act as catalytic ATP-competitive inhibitors. These compounds showed promising cytotoxicity against selected cancer cell lines, did not induce DNA double-strand breaks, and arrested the cell cycle mainly in the G1 phase. This confirmed the mechanism of action, which is also different from that of topoisomerase poisons at the cellular level [4].

Human topoisomerase IIα was also used as a model target for a dynophore-based approach to molecular design. Based on molecular simulations of a known catalytic inhibitor and the native ATP ligand analogue AMP-PNP, we derived a joint dynophore model that complements the static structure-based pharmacophore information with a dynamic component. The derived pharmacophore models were used in a virtual screening campaign of a library of natural products. Experimental evaluation identified flavonoid compounds with catalytic topo IIα inhibition and confirmed binding to its ATPase domain, validating the utility of the developed molecular design strategy [5].



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